European Association of Urology

EUROPEAN UROLOGY SUPPLEMENTS

Insights into the Relationships between Prostatic Disorders and Their Potential Impact on Future Urologic Practice

Claus Roehrborn *

Department of Urology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., J8 142, Dallas, TX 75390-9110, United States

Article info

EU★ACME
www.eu-acme.org

Please visit
www.eu-acme.org to read
and answer the EU-ACME
questions on-line. The
EU-ACME credits will then
be attributed automatically.

Abstract

Although the relationship between increasing age and the prevalence of histologic benign prostatic hyperplasia (BPH), prostate inflammation, high-grade intraepithelial neoplasia, atypical small acinar proliferation, and prostate cancer has been understood for some time, our understanding of the interrelationships between prostate diseases beyond epidemiologic associations is evolving. Furthermore, we are just beginning to unravel how these relationships may affect ageing men, in terms of their effects on bladder function, resultant lower urinary tract symptoms, sexual dysfunction, and overall quality of life. There is increasing evidence of a role for inflammation in the development of prostate cancer and also in precipitating symptoms and acute urinary retention in men with BPH. Furthermore, experimental and clinical trial evidence demonstrates the importance of androgens, particularly dihydrotestosterone, in the development and maintenance of a number of prostate disorders. Although the theoretical role of the 5α-reductase inhibitors in the prevention of prostate cancer was hypothesised almost 20 yr ago, it was not until recently that the Prostate Cancer Prevention Trial demonstrated their benefit. Taken together with their effects on BPH, and putative benefits on chronic prostate inflammation, it is possible that the 5α-reductase inhibitors may have a broader role in the maintenance of prostate health and that they could provide concomitant benefits across a wider spectrum of prostate disease. Such a strategy has profound implications for the screening, detection, and long-term management of prostate disease in ageing men.

* Tel. +1 214 648 2941; Fax: +1 214 648 0365.
E-mail address: claus.roehrborn@utsouthwestern.edu.

1. Introduction

Our views on prostate health and disease in ageing men are changing. In the past, we have considered histologic benign prostatic hyperplasia (BPH), prostate inflammation, high-grade intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP), and prostate cancer as having epidemiologic relationships, principally their association with increasing age [1–3]. However, our understanding of the interrelationships between prostate diseases beyond epidemiologic associations is

evolving, and pathologic links between these disorders are emerging. The overlay of different pathologic mechanisms within the prostate, for example, inflammation and hyperplasia, may produce clinical profiles that reflect the underlying pathology. We are just beginning to unravel how these relationships may ultimately affect ageing men, not only in symptomatic terms for their effects on bladder function, resultant lower urinary tract symptoms (LUTS), sexual dysfunction, and overall quality of life, but also ultimately their risk for developing premalignant conditions and prostate cancer. This article explores these relationships and examines the implications they may have for the future management of prostate health in the ageing man.

2. BPH, detrusor instability, and LUTS

2.1. Epidemiology and natural history

The association of histologic BPH with increasing age has been confirmed by many epidemiologic studies, with the prevalence reaching almost 100% in the most elderly men [4]. The equally well-documented association of LUTS with increasing age, with the prevalence of significant symptoms increasing in a linear fashion [4,5], is often attributed to underlying BPH. However, it is becoming evident that such a view may be overly simplistic. Men with LUTS often have both storage symptoms (frequency, urgency, incontinence, nocturia, and pain) as well as emptying symptoms (weak stream, hesitancy, incomplete emptying, urinary retention, postvoid dribbling, and pain), and therefore have symptoms concordant with detrusor instability. Indeed the National Overactive Bladder Evaluation (NOBLE) study unexpectedly demonstrated that the prevalence of overactive bladder (OAB) is similar in men and women, although the classic symptom of urge incontinence was found in only 16% of men versus 55% of women [6]. Taken together, these data suggest a significant epidemiologic relationship between bladder outlet obstruction (BOO), detrusor overactivity, and LUTS in ageing men. Such a relationship has recently been confirmed in a study of 114 men, which demonstrated that men with detrusor overactivity and a positive ice water test (IWT) had greater mean prostate volume, prostate-specific antigen (PSA) and BOO index values, and lower maximum flow rate (Q_{max}) than those without overactivity and with a negative IWT [7].

2.2. Pathologic linkage

From the discussion above, it appears likely that LUTS in ageing men can be caused by overlapping pathophysiologic mechanisms, with detrusor instability playing a part in addition to BOO from BPH. It has been hypothesised that such mixed pathophysiology may contribute to individual variation in response to treatment and may explain why LUTS are not fully ameliorated in a significant minority of men following prostatectomy [8], although detrusor underactivity may also play a role in long-term treatment failure [9]. If this hypothesis is correct, it could be expected that combining agents with recognised benefits in BOO and OAB may be beneficial in men in whom concomitant pathophysiologic mechanisms are evident. This hypothesis has been examined in a study of 144 men with BOO and LUTS who were divided into two groups based on the presence or absence of involuntary detrusor contractions [10]. The response to α-blocker therapy was markedly lower at 3 mo in men with BOO and OAB versus those with BOO alone (35% with BOO and OAB reported symptomatic improvement versus 79% with BOO alone). Among those with no improvement in symptoms at 3 mo, 73% of those with BOO and OAB improved with the addition of tolterodine versus 38% of those with BOO alone. Although these data are from a small and nonrandomised study, they do suggest that OAB may contribute to LUTS in some men with BOO [11].

3. BPH and prostatitis

3.1. Epidemiology and natural history

It is intuitive that prostatitis and BPH are likely to coexist in ageing men, and indeed, epidemiologic data suggest that this is the case. One study identified that among those with self-reported prostatitis, 57% had a history of BPH compared with 17% of those who did not report prostatitis [2]. These data are supported by those of a recent large-scale study, which demonstrated that men with a history of prostatitis were twice as likely to have a history of BPH, and had significantly higher scores on the American Urological Association Symptom Index (AUA-SI) [12]. Conversely, in a recent analysis of a study that recruited 5096 men from a number of countries, about 20% of those sexually active men with LUTS suggestive of BPH reported pain or discomfort on ejaculation [3]. These men had more severe LUTS, greater bother, and a higher prevalence of sexual dysfunction than those without symptoms suggestive of prostatitis. Furthermore, on histologic analysis, prostatitis was found to be associated with BPH, with an

increased prostate volume associated with their coexistence [13].

3.2. Pathologic linkage

The epidemiologic data suggest that men with coexistent BPH and prostatitis are likely to have more severe, progressive BPH. To clarify the relationship between prostate inflammation and BPH, a biopsy substudy of the Medical Therapy of Prostatic Symptoms (MTOPS) study ($n = 1198$), of whom 45% had evidence of acute (2.6%) or chronic (42.8%) prostatic inflammation, has recently been completed [14]. Men with inflammation had a significantly higher mean prostate volume (41.1 vs. 36.8 cc) and serum PSA (3.3 vs. 2.5 ng/ml) compared with those without inflammation. Furthermore, from an outcome perspective, patients in the placebo group with inflammation were more likely to have BPH progression than those without inflammation (21.0% with inflammation had an event vs. 13.2% without inflammation). Although a rise in AUA-SI was marginally more likely in men with inflammation versus those without (13.7% vs. 11.2%), the most striking finding was the lack of acute urinary retention (AUR) events in men without inflammation compared with a 5.6% risk in those with inflammation ($p = 0.011$; Fig. 1). These data, for the first time, provide evidence of the role of inflammation in BPH, demonstrating that the presence of chronic inflammation may be a key factor in BPH progression.

4. Prostatitis and prostate cancer

4.1. Epidemiology and natural history

Another epidemiologic relationship that has recently been examined in greater detail is the association between prostate inflammation and prostate cancer. Prostate cancer remains by some margin the most common malignancy in men, and although mortality is lower than in other common malignancies, prostate cancer is the second most common cause of malignant death in men [15]. The almost ubiquitous nature of prostate cancer in the "old old" has been documented from autopsy studies for many years, although the prevalence has decreased in the PSA era [16]. The true prevalence of infectious and noninfectious prostatitis has been more difficult to gauge: prostatitis-like symptoms are reported to occur in 5–10% of men [17]; however, diagnosed prostatitis in a clinic population is on the order of 3% [18]. Data examining
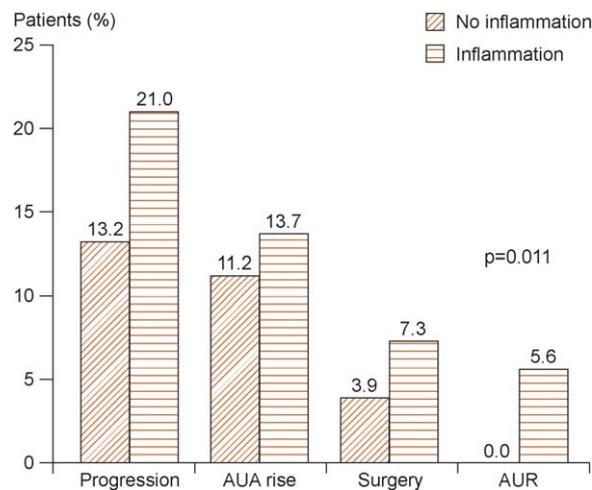
Fig. 1 – Progression events in the Medical Therapy of Prostatic Symptoms study by the presence or absence of inflammation on biopsy [14].

epidemiologic links between prostate cancer and prostatitis are limited because of the high prevalence of prostatitis in biopsy specimens [19] and the increased likelihood of a biopsy in men with prostatitis symptoms [20]. A further confounding issue is the observation that prostatitis symptoms are poorly correlated with the prevalence of inflammation in prostate biopsies [21]. However, evidence from epidemiologic studies suggests that prior prostatitis is indeed a marker for the development of prostate cancer [12,22].

4.2. Pathologic linkage

Although the role of inflammation in the pathogenesis of prostate cancer has not been fully defined, a number of potential mechanisms exist that suggest such a link (Fig. 2) [20,23]. For example, the association between sexually transmitted infections (regardless of the pathogen involved) and the incidence of prostate cancer suggest a link [24]. Interestingly, two genes that are candidates for prostate cancer susceptibility, MSR1 and RNASEL, both encode proteins involved in the host response to infection [25,26]. In the late 1990s, it was proposed that proliferative inflammatory atrophy (PIA), a lesion commonly found in the prostate periphery, may, in fact, be a precursor to prostate cancer [27]. These areas of atrophy, which contain proliferative epithelial cells that do not differentiate into columnar cells, have been observed adjacent to both PIN and cancer and also contain somatic gene abnormalities similar to these cell types [28]. The hypothesis is that PIA occurs as a response to oxidants released during inflammation, and, indeed, these lesions
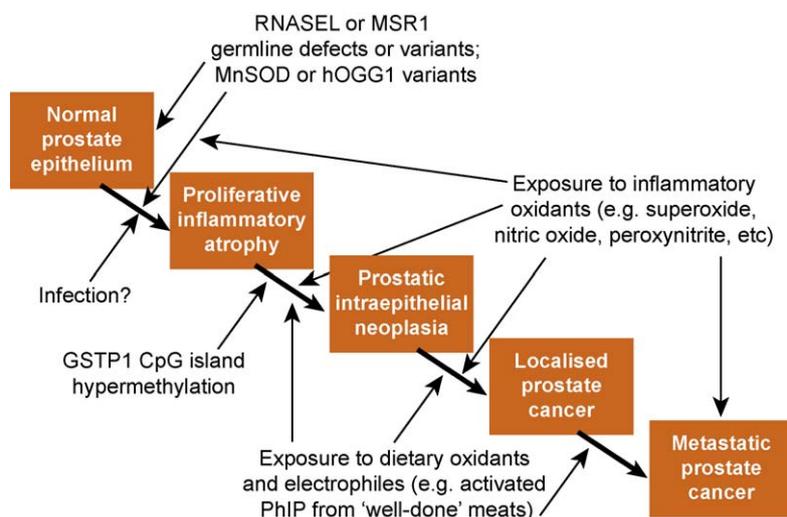
Fig. 2 – Hypothetical role of inflammation as a precursor to prostate cancer [20].

show evidence of expression of glutathione S-tranferases and cyclooxygenase-2, both of which are expressed in cells where oxidative stress is present [29,30]. At this time, though, we lack definitive proof that infection or inflammation has a role in the pathogenesis of prostate cancer, and this area therefore warrants further scrutiny [31].

## 5.   Implications for urologic practice

These observations have a number of implications for clinical practice. First, prostatic inflammation is a potential confounder in the diagnosis of prostate disease because the presence of inflammation does not correlate with symptoms [21], and furthermore, men with prostate inflammation are more likely to have a higher PSA value, potentially confounding prostate cancer screening [32]. Second, the observation that the manifestations of prostate pathology may reflect a continuum of progressive disease, with interrelationships between inflammation and benign and malignant growth of the prostate, suggests that earlier, preventive therapy may have a role in the maintenance of prostate health.

The central role of androgen stimulation in the development of prostate disease suggests that inhibition of 5α-reductase may have a role in restoring the imbalance between cell proliferation and death seen in the development of prostate disorders. Studies in cell lines, animals, and humans have confirmed that 5α-reductase inhibitors (5-ARIs) have a significant benefit in ameliorating prostate epithelial proliferation and enhancing apoptosis [33–35]. The clinically demonstrated benefits of these effects include the treatment of symptoms and prevention of BPH progression to AUR and BPH-related surgery through sustained reductions in prostate volume [36–38]. The role of OAB in BPH symptomatology needs further exploration; it may be that subsets of men with LUTS require more complex medical management to ensure long-term amelioration of their symptoms, in addition to the preventive and symptomatic benefits observed with 5-ARI therapy and the symptomatic benefits observed with α-blocker therapy.

In theory, reduction of the androgenic drive to the prostate through 5α-reductase inhibition could have a number of potential benefits in men with chronic, nonbacterial prostatitis. First, the 5-ARIs are known to reduce prostate volume, which could have an impact on BOO associated with prostatic inflammation. Second, evidence from animal models of chronic prostatitis indicates that the balance between androgens and oestrogens may influence not only the development but also the persistence and degree of severity of the disease [39]. During the Prostate Cancer Prevention Trial (PCPT), there was a lower prevalence of prostatitis in the finasteride group versus the placebo group (6.1% vs. 4.4%), suggesting that these theoretical effects may result in clinical benefits [40]. However, the PCPT was not designed to examine this issue directly.

A recent pilot study has been completed to compare 6 mo of finasteride treatment and placebo in men with National Institutes of Health (NIH) IIIA (chronic inflammatory) prostatitis [41]. This small study demonstrated a lower symptom score at 6 mo in men treated with finasteride versus placebo. Another small-scale study, which recruited men with NIH III prostatitis, compared daily finasteride treatment with saw palmetto over 1 yr of therapy [42].
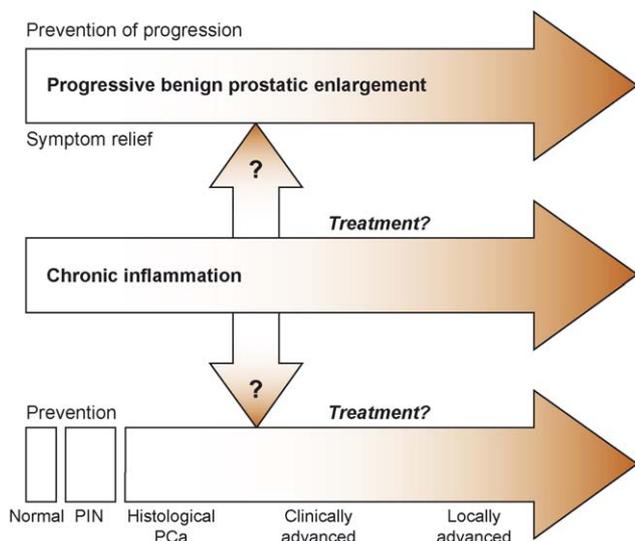
Fig. 3 – Demonstrated (bold) and putative (italics) role of 5α-reductase inhibitors in the management and prevention of prostate disease.

Symptom scores were reduced from baseline to end point in the finasteride group but not in the saw palmetto group. Much additional work is needed to establish the roles of androgens in the development and maintenance of prostatitis, and data from large-scale studies are needed to clarify the apparent effect of 5-ARIs in its management. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, which is examining the potential of dutasteride in the chemoprevention of prostate cancer over 4 yr, is also evaluating its effects on prostatitis using the NIH Chronic Prostatitis Symptom Index and histopathologic evaluation and may shed further light on the role of 5-ARIs in the treatment of prostatitis [43].

The theoretical role of 5-ARIs in the prevention of prostate cancer was hypothesised almost 20 yr ago, but it was not until recently that the PCPT has demonstrated that the type-2 selective 5-ARI, finasteride, reduces the 7-yr prevalence of prostate cancer in a broad population of men [40]. Taken together with their effects on BPH, and putative benefits on chronic prostate inflammation, it is possible that the 5-ARIs may have a broader role in the maintenance of prostate health and that they could provide concomitant benefits across a wider spectrum of prostate disease (Fig. 3). The 5-ARIs may, therefore, be able to offer both active treatment (BPH, prostatitis) and prevention (BPH progression, transition from benign tissue to HGPIN to prostate cancer). Such strategies have profound implications for the screening, detection, and long-term management of prostate disease in ageing men.

References

[1] Bostwick DG, Burke HB, Djakiew D, et al. Human prostate cancer risk factors. Cancer 2004;101:2371–490.
[2] Collins MM, Meigs JB, Barry MJ, et al. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. J Urol 2002;167:1363–6.
[3] Nickel JC, Elhilali M, Vallancien G. Benign prostatic hyperplasia (BPH) and prostatitis: prevalence of painful ejaculation in men with clinical BPH. BJU Int 2005;95:571–4.
[4] Emberton M, Andriole GL, de la Rosette J, et al. Benign prostatic hyperplasia: a progressive disease of aging men. Urology 2003;61:267–73.
[5] Nørby B, Nordling J, Mortensen S. Lower urinary tract symptoms in the Danish population: a population-based study of symptom prevalence, health-care seeking behavior and prevalence of treatment in elderly males and females. Eur Urol 2005;47:817–23.
[6] Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327–36.
[7] Hirayama A, Fujimoto K, Matsumoto Y, Hirao Y. Nocturia in men with lower urinary tract symptoms is associated with both nocturnal polyuria and detrusor overactivity with positive response to ice water test. Urology 2005;65:1064–9.
[8] Andersson KE. Storage and voiding symptoms: pathophysiologic aspects. Urology 2003;62:3–10.
[9] Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic followup of transurethral resection of prostate for bladder outlet obstruction. J Urol 2005;174:1887–91.
[10] Lee JY, Kim HW, Lee SJ, et al. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int 2004;94:817–20.
[11] Ruggieri Sr MR, Braverman AS, Pontari MA. Combined use of alpha-adrenergic and muscarinic antagonists for the treatment of voiding dysfunction. J Urol 2005;174:1743–8.
[12] Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC. Correlates and prevalence of prostatitis in a large community-based cohort of older men. Urology 2005;66:964–70.
[13] Gerstenbluth RE, Seftel AD, MacLennan GT, et al. Distribution of chronic prostatitis in radical prostatectomy specimens with up-regulation of bcl-2 in areas of inflammation. J Urol 2002;167:2267–70.
[14] Roehrborn CG, Kaplan SA, Noble WD, et al. The impact of acute or chronic inflammation in baseline biopsy on the risk of clinical progression of BPH: results from the MTOPS study. Abstract presented at the American Urological Association Annual Meeting, San Antonio, TX, 21–26 May 2005.
[15] Cancer Facts and Figures 2005. Atlanta, GA: American Cancer Society; 2005.
[16] Konety BR, Bird VY, Deorah S, Dahmoush L. Comparison of the incidence of latent prostate cancer detected at autopsy before and after the prostate specific antigen era. J Urol 2005;174:1785–8, discussion 1788.

[17] Krieger JN, Riley DE, Cheah PY, Liong ML, Yuen KH. Epidemiology of prostatitis: new evidence for a world-wide problem. World J Urol 2003;21:70–4.

[18] Nickel JC, Teichman JM, Gregoire M, Clark J, Downey J. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE Study. Urology 2005;66:935–40.

[19] Carver BS, Bozeman CB, Williams BJ, Venable DD. The prevalence of men with National Institutes of Health category IV prostatitis and association with serum prostate specific antigen. J Urol 2003;169:589–91.

[20] Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. J Urol 2004;172:S6–11, discussion S-2.

[21] Nickel JC, Bostwick D, Sommerville M, Rittmaster R. Lack of relationship between clinical prostatitis and prostate inflammation: baseline data from the REDUCE trial. Abstract presented at the International Consultation on Prostatic Diseases, Paris, France, 24–27 June 2005.

[22] Roberts RO, Bergstralh EJ, Bass SE, Lieber MM, Jacobsen SJ. Prostatitis as a risk factor for prostate cancer. Epidemiology 2004;15:93–9.

[23] Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med 2003;349:366–81.

[24] Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology 2002;13:72–9.

[25] Carpten J, Nupponen N, Isaacs S, et al. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet 2002;30:181–4.

[26] Platt N, Gordon S. Is the class A macrophage scavenger receptor (SR-A) multifunctional? The mouse's tale. J Clin Invest 2001;108:649–54.

[27] De Marzo AM, Marchi VL, Epstein JI, Nelson WG. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. Am J Pathol 1999;155:1985–92.

[28] Shah R, Mucci NR, Amin A, Macoska JA, Rubin MA. Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? Am J Pathol 2001;158:1767–73.

[29] Parsons JK, Nelson CP, Gage WR, et al. GSTA1 expression in normal, preneoplastic, and neoplastic human prostate tissue. Prostate 2001;49:30–7.

[30] Zha S, Gage WR, Sauvageot J, et al. Cyclooxygenase-2 is up-regulated in proliferative inflammatory atrophy of the prostate, but not in prostate carcinoma. Cancer Res 2001;61:8617–23.

[31] Thompson IM, Albanes D, Basler JW, et al. First International Conference on Chemoprevention of Prostate Cancer. Overview consensus statement. J Urol 2004; 171:S3–4.

[32] Simardi LH, Tobias-MacHado M, Kappaz GT, et al. Influence of asymptomatic histologic prostatitis on serum prostate-specific antigen: a prospective study. Urology 2004;64:1098–101.

[33] Rittmaster RS, Norman RW, Thomas LN, Rowden G. Evidence for atrophy and apoptosis in the prostates of men given finasteride. J Clin Endocrinol Metab 1996; 81:814–9.

[34] Glassman DT, Chon JK, Borkowski A, Jacobs SC, Kyprianou N. Combined effect of terazosin and finasteride on apoptosis, cell proliferation and transforming growth factor-beta expression in benign prostatic hyperplasia. Prostate 2001;46:45–51.

[35] Festuccia C, Angelucci A, Gravina GL, et al. Effects of 5 alpha reductase inhibitors on androgen-dependent human prostatic carcinoma cells. J Cancer Res Clin Oncol 2005;131:243–54.

[36] McConnell JD, Bruskewitz R, Walsh PC, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998;338: 557–63.

[37] McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349:2387–98.

[38] Roehrborn CG, Marks LS, Fenter T, et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. Urology 2004;63:709–15.

[39] Nickel JC. The role of the animal model in the study of prostatitis. In: Bergan T, editor. Urinary tract infection. Basel: Karger; 1997. p. 89–97.

[40] Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride in the development of prostate cancer. N Engl J Med 2003;349:215–24.

[41] Nickel JC, Downey J, Pontari MA, Shoskes DA, Zeitlin SI. A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). BJU Int 2004;93:991–5.

[42] Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 2004;171:284–8.

[43] Andriole G, Bostwick D, Brawley O, et al. Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial. J Urol 2004;172:1314–7.