

Understanding the Epidemiology, Natural History, and Key Pathways Involved in Prostate Cancer

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Prostate cancer accounts for about 25% of all the newly diagnosed cancers in American men and was projected to cause >28 000 deaths in 2008. Black men are disproportionately affected; their incidence rate is about 1.6 times greater than the rate for white men. As the population ages, the number of new cases per year is expected to increase by >60% and reach 300 000 by 2015. This high incidence, coupled with the protracted onset of the disease, makes PCa a particularly appropriate candidate for prevention and early intervention strategies. Potential disease precursors, particularly high-grade prostatic intraepithelial neoplasia, might help identify men at high risk of developing PCa. Dihydrotestosterone, a product converted from testosterone by 5α -reductases, plays an important role in normal prostate growth and in the development of PCa. The 5α -reductase levels, particularly type 1, appear to increase during the disease course of prostatic intraepithelial neoplasia and PCa, with greater expression occurring as the disease progresses. Therefore, the inhibition of 5α -reductase could potentially reduce the risk of PCa development, slow or prevent disease progression, and/or treat existing disease. A substantial research effort has recently focused on understanding the pathways involved in the disease's emergence and progression, particularly the 5α -reductase pathway. UROLOGY 73 (Suppl 5A): 4–10, 2009. © 2009 Published by Elsevier Inc.

EPIDEMIOLOGY OF PROSTATE CANCER

Prevalence and Incidence

Globally, prostate cancer (PCa) is highly prevalent. It is the most common noncutaneous cancer in men.^{1,2} An estimated 782 600 new cases and 254 000 deaths caused by the disease occurred in 2007.³ The mortality rates for PCa have been decreasing in many developed countries (eg, the United States, the United Kingdom, and Canada), which has been attributed to improved treatment and early detection.^{3,4} In contrast, PCa mortality has been increasing in some Asian countries (eg, Japan, Singapore). The list of likely causes includes increased consumption of animal fat, obesity, and physical inactivity.³

In the United States, in 2008, new cases of PCa were projected to account for approximately 25% (186 320) of all cancers diagnosed in men.¹ Despite the advances in early detection, PCa continues to cause substantial mortality in the United States.^{1,2} It ranked second (10%; 28 660) among the 10 leading cancer-related causes of death for men in 2008; cancer of the lung and bronchus were first (31%; 90 810). In the United States, the 5-year survival rate

for localized or regional PCa is 100%. However, when it has already metastasized by the time of diagnosis, the 5-year survival rate has been as low as 32%.¹

The incidence of PCa generally increases with increasing age.^{2,5,6} According to 1 analysis of U.S. incidence data from 2001 to 2005, approximately 37% of cases of PCa were diagnosed in men <65 years old. Between the ages of 45 and 54 years, the percentage of diagnosed cases increased to 8.6% from almost no cases in younger age cohorts. The largest percentage of diagnosed cases was found in those 65–74 years old (36% of all cases); 22% of all cases occurred in men 75–84 years old, and roughly 5% of cases were found in those ≥ 85 years old.² Prostatic tissue samples from autopsies of a mostly white male population with no history of intervention related to prostatic disease revealed an age-dependent increase in PCa. In that study, about 35% of those men 60–69 years old and 46% of those 70–81 years old had PCa.⁶ The United States is likely to see a large increase in the prevalence of PCa as the population ages.

Incidence Among Men of Different Racial Backgrounds

The incidence of PCa varies by race and ethnicity in the United States.^{7,8} Black men, in particular, appear to be disproportionately affected.² A prospective study of heart disease and cancer among male healthcare professionals found an age-adjusted rate ratio for PCa of 1.73 to 1 for black vs white men. The increased risk of PCa among black men remained elevated even after adjusting for dietary and lifestyle risk factors.⁸

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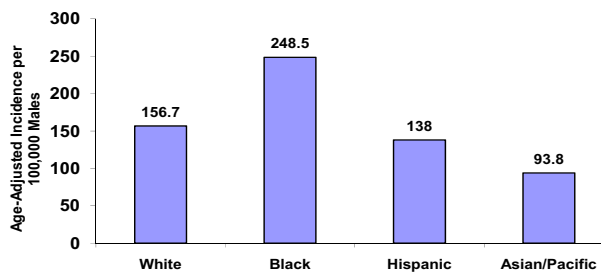


Figure 1. Age-adjusted incidence of prostate cancer among different racial/ethnic populations of men (2001-2005). Data from Ries et al.²

Figure 1 summarizes the age-adjusted incidence of PCa by race/ethnicity in the United States from 2001 to 2005. PCa was nearly 1.6 times more common in black men than in white men.² Black men were also twice as likely as white men to die of PCa.⁹ Black men were at the upper end of the PCa incidence spectrum in the United States, and the next-highest incidence was in white men. As seen in Figure 1, the age-adjusted incidence of PCa was lower among men of Hispanic, Asian/Pacific Islander, and Native American/Alaskan Native ethnicity than among white men.

These disparities might be related to differences in the environment (eg, exposure, diet), detection, genetic background, or physiologic status (eg, sex steroid hormone levels).^{7,10,11} A role for environmental factors (particularly diet) has been suggested by the observation that the PCa incidence increased considerably in Japanese men who moved from Japan to the United States.¹² Studies examining the effects of diet on PCa risk have yielded inconsistent results. For example, an analysis of data from the Cancer Prevention Study II Nutrition Cohort identified an association between total red meat intake and the risk of PCa in black men, but not in white men.¹³ Another study, the Multiethnic Cohort Study, failed to demonstrate an association between fat/meat uptake and PCa risk in any of the 4 racial/ethnic groups studied (blacks, Japanese Americans, Latinos, and whites).¹⁴

NATURAL HISTORY AND PATHOPHYSIOLOGY OF PCa

Natural History

Our understanding and narrative of PCa's natural history is far from complete. This is partly because the disease is heterogeneous in both morphology and clinical behavior.¹⁵ About one third of all American men >50 years old have histologic evidence of PCa; however, most of these cases remain clinically "silent." Multiple genetic changes appear to be necessary for clinically aggressive PCa to develop.¹⁶

How the disease develops when localized varies. Lower grade tumors (ie, highly or moderately differentiated tumors) tend to have a more protracted course. In contrast, some high-grade tumors progress more rapidly to meta-

static disease.^{17,18} A pooled analysis of 828 patients from 6 nonrandomized studies found that highly or moderately differentiated tumors yielded a 10-year disease-specific survival rate of 87%, but poorly differentiated tumors were associated with a 34% survival rate. Similarly, the 5- and 10-year metastasis-free survival rates were greater among men with lower disease grades (ie, grades indicating greater differentiation).¹⁷

A population-based cohort study examined the natural history of untreated, early-stage PCa during a mean observation period of 21 years. The study included 223 patients (mean age 72 years, range 41-91). Of these patients, 106 cases of PCa were detected by examination of the histologic specimens collected during operations performed because of suspected benign prostatic hyperplasia, and 117 were identified as palpable clinical disease that was localized to the prostate. The disease progressed in 89 patients (40%), and 39 (17% of the cohort) developed metastatic disease. However, the study did not consider PCa cases detected through prostate-specific antigen (PSA) testing, because it had not been available at the time of diagnosis, and PSA screening did not occur during the period when this cohort had been recruited (1977-1984). In most cases, the disease moved slowly during the first 10-15 years after diagnosis.¹⁸ As reported by Chodak et al.,¹⁷ tumors that were highly differentiated at diagnosis were associated with lower rates of progression and PCa death. However, 15-20 years after diagnosis, substantial decreases occurred in the cumulative progression-free survival (from 45.0% at 15 years to 36.0% at 20 years), metastasis-free survival (from 76.9% to 51.2%), and PCa-specific survival (from 78.7% to 54.5%) rates. An increase in PCa mortality rate was also seen between the first 15 years of follow-up (15 per 1000 person-years) and the subsequent follow-up (44 per 1000 person-years).¹⁸ These findings highlight the importance of time in the development of PCa—time that offers opportunities for interventions (strategies to prevent or reduce risk) that might be able to alter the usual course, the standard natural history, of the disease.

Pathophysiology of PCa

Almost all cases of PCa are adenocarcinoma.^{15,19} About 4% of PCa cases exhibit transitional cell morphology and are believed to have developed from the urogenital lining of the prostatic urethra. Few cases of PCa have neuroendocrine morphology. These are thought to derive from either neuroendocrine stem cells normally present in the prostate or processes of aberrant transformation that occur during cell transformation.²⁰

Figure 2 illustrates the different zones of the prostate.¹⁵ In the young adult, the transition zone typically constitutes about 5%-10% of the mass of the glandular prostate and surrounds the urethra proximal to the entry of the ejaculatory ducts. The central zone accounts for approximately 20%-25% of the mass of the normal glandular prostate and is positioned below the proximal urethral

segment.^{15,21} The ejaculatory ducts pass through the central zone before entering the urethra.¹⁵ About 70%-75% of the normal glandular structure of the adult prostate consists of the peripheral zone, a double row of duct buds that surround the central zone laterally and occupy the apical region of the prostate. The anterior fibromuscular stroma is nonglandular and constitutes about one third of the mass within the prostatic capsule.^{15,21} This anatomic region is intermingled, with fibers descending from the bladder neck, as well as from the striated urethral sphincter.¹⁵

The transitional zone and other periurethral glands are where benign prostatic hyperplasia (BPH) develops.²¹ Most PCa cases (about 70%) begin in the peripheral zone.^{15,20,21} About 10%-15% of PCa cases develop in the transitional zone and 15%-20% in the central zone.²⁰ Most cases are multifocal (ie, multiple independent malignant clones are present in the same gland). These multicentric lesions are often present in different zones of the prostate and typically are of different grades.^{19,22,23} Because multicentric lesions can have different characteristics, one cannot be sure that the characteristics of a carcinoma identified at biopsy represent the status of the gland as a whole until the prostate has been removed and thoroughly examined.¹⁹

UNDERSTANDING THE MECHANISMS INVOLVED IN DEVELOPMENT AND PROGRESSION OF PCa

Current Understanding of Prostate

Growth: Role of Dihydrotestosterone

Testosterone is the main circulating androgen in men.²⁴ In the prostate and other organs, testosterone functions as a prohormone; it is converted to dihydrotestosterone (DHT) in the prostatic stromal and basal cells by 5 α -reductase (5AR), an intracellular enzyme present in the prostate, skin, and liver.^{24,25} In serum, the ratio of testosterone to DHT is approximately 10:1. This ratio is reversed in the prostate.²⁶

DHT is the primary prostatic androgen and plays an essential role in prostate development and growth. DHT has as much as 10 times more affinity for the androgen receptor (AR) than does testosterone.²⁷ DHT exhibits different functions according to the developmental stage of an individual. In utero, DHT plays a critical role in the normal differentiation of the male external genitalia and prostate. Evidence supporting the role of DHT in prostate development derives from observations of the Guevedoce (Dominican pseudohermaphrodites), a population characterized by male internal urogenital tracts but female-appearing external genitalia until age 12 and small prostates as adults.^{26,28,29} In Guevedoce, 5AR is deficient.^{26,30} The testosterone levels are normal, but the DHT levels are markedly suppressed.²⁸ Prostatic diseases such as PCa and BPH have not been reported in these individuals, an important consequence of suppressed

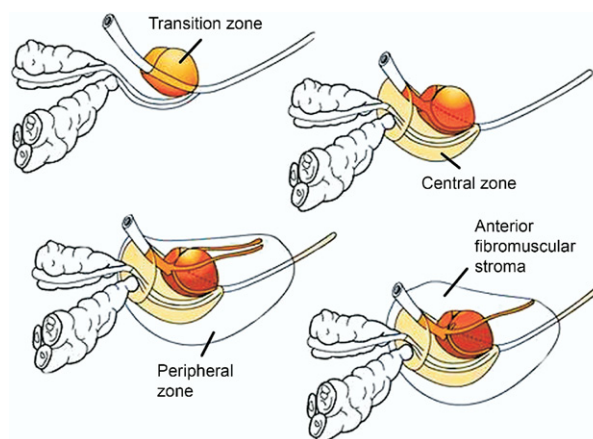


Figure 2. Different zones of prostate. Adapted with permission, from Greene et al.^{15a} © Elsevier.

DHT levels. Administration of DHT can produce enlargement of the prostate in these individuals, underscoring the role of DHT in prostate development. DHT is also responsible for facial hair, acne, male pattern baldness, and prostate growth.^{26,29}

5 α -Reductase

Three isoforms of 5AR have been identified; a separate gene encodes each isoform.³¹⁻³³ The type 1 isoform is prevalent in extraprostatic tissue (ie, nongenital skin, liver, and certain brain regions) and is present throughout life. Although conflicting results have been reported,²⁵ several studies have suggested that type 1 5AR is also expressed in the prostate and preputial skin. This isoform appears to be most strongly expressed in the prostatic epithelium and predominantly localized in nuclei of luminal secretory cells.³⁴⁻³⁶ Its expression increases in PCa (relative to BPH tissue).³⁵ Its expression is low in BPH tissue but increases steadily in prostatic intraepithelial neoplasia and in primary, recurrent, and metastatic PCa.³⁷

Type 2 5AR is prevalent in the prostate and is also present in the seminal vesicles and epididymis, as well as in the fetal genital skin. In the skin and scalp, a single wave of expression of type 2 5AR begins at or just before birth and ends at around 2-3 years of age.²⁵ The type 2 isoform is deficient in the Guevedoce owing to a deletion in the gene.^{26,30}

Recently, a novel 5AR (type 3) has been reported specifically in hormone-refractory PCa cells with little or no expression in normal adult organs; it appears to play a role in hormone-refractory PCa growth and progression.³³ Its potential role as a therapeutic target in PCa remains to be elucidated.

The activity of 5AR is different in various ethnic groups and greater among groups with greater rates of PCa.³⁸ Studies indirectly estimating 5AR activity by measuring levels of 5 α -reduced androgen metabolites have provided evidence of elevated 5AR activity among white men compared with Chinese-American

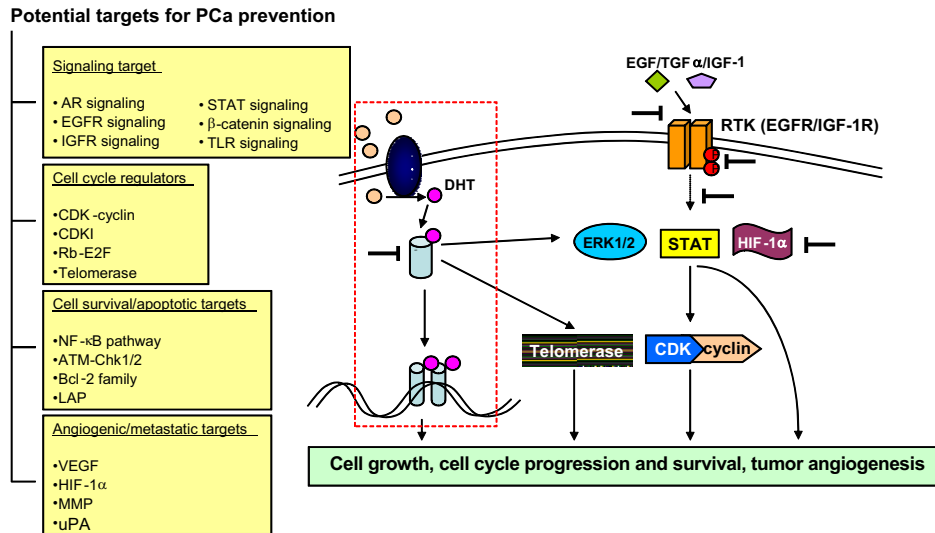


Figure 3. Pathways involved in prostate cancer (PCa) growth and progression. **(Left)** Summary of biochemical pathways that are potential targets for PCa intervention and risk reduction. **(Right)** Androgen receptor (AR) and receptor tyrosine kinase signaling targeted by therapeutic agents to inhibit cell growth, deregulated cell cycle progression, and cell survival. Sideways T indicates areas in which intervening in cellular pathways of disease might be possible. Dashed rectangle outlines process by which 5 α -reductase converts testosterone to dihydrotestosterone (DHT), which binds to ARs, leading to nuclear translocation and transcriptional activation of androgen-responsive genes. Potential interaction with other signaling pathways, such as ERK1/2, also displayed. 5 α R, 5 α -reductase; CDK, cyclin-dependent kinase; CDKI, cyclin-dependent kinase inhibitor; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; HIF-1 α , hypoxia-inducible factor-1 α -subunit; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; IGFR, insulin-like growth factor receptor; LAP, leucine aminopeptidase; MMP, matrix metalloproteinase; NF- κ B, nuclear factor kappa B; Rb-E2F, retinoblastoma; RTK, receptor tyrosine kinase; STAT, signal transducers and activators of transcription; TGF α , transforming growth factor α ; TLR, toll-like receptors; uPA, urokinase plasminogen activator; VEGF, vascular endothelial growth factor. Adapted, with permission, from Singh and Agarwal.⁴² ©Society for Endocrinology.

men³⁹ and among white and black men compared with Japanese American men.³⁸ In 1995, Wu et al.⁴⁰ calculated the DHT-to-testosterone ratios to indirectly measure the activity of 5AR. Although large differences were not seen in the absolute value of the DHT-to-testosterone ratio among ethnic groups, the ratio was greatest among blacks, intermediate among whites, and lowest among Japanese Americans and Chinese Americans. The DHT-to-testosterone ratio was significantly lower among Chinese Americans than among whites and blacks ($P < .01$), but the difference between blacks and whites did not reach significance. The relative differences in the DHT-to-testosterone ratios reflected the PCa incidence rates in these ethnic groups. The DHT-to-testosterone ratio was also lower among Asia-born Asians than among Asians born in North America (difference not significant),⁴⁰ which is notable considering the greater incidence rates of PCa that have been observed among some Asian men—Japanese-born—who moved from Japan to the United States.¹² More recently, a study of a community-based sample of 1899 men in Boston, 30-79 years of age, reported significantly greater DHT-to-testosterone ratios in black men than in white and Hispanic men, suggesting greater 5AR activity among black men.⁴¹

Pathways Involved in Cancer Growth and Progression

The development and progression of PCa is a complex process that involves interactions between AR-mediated signaling and receptor tyrosine kinase signaling. Figure 3 illustrates the pathways involved in cancer growth and progression. The molecular components of these pathways include cell signaling, cell cycle regulators, cell survival/apoptotic molecules, and angiogenic and metastatic targets.⁴²

AR signaling plays a pivotal role in both the growth of PCa and the development of hormonal resistance and disease relapse. DHT binds to the AR, inducing the DHT-AR complex to translocate into the nucleus and activate transcription of androgen-responsive genes.^{37,42} In the normal prostate, DHT stimulates prostatic epithelial cell function, promoting epithelium growth while inhibiting cell death.⁴³ The AR is expressed throughout the progression of PCa, and this progression typically persists in patients with hormone-refractory disease.⁴⁴ During disease progression, prostate tumors progress from androgen dependent to androgen independent (hormone refractory).³⁷ Evidence has suggested that the following processes involving the AR contribute to the progression of PCa: (a) alteration of the normal androgen axis by way of dysregulation of AR activity by signal transduction

cascades; (b) changes in the expression of co-regulators of the AR; and (c) mutations of the AR that allow it to be activated by ligands, in addition to testosterone and DHT, thus potentially contributing to androgen independence.⁴⁴

Growth factors and receptor tyrosine kinase signaling contribute to the development and progression of PCa through interactions with AR signaling, as well as by independent pathways. Binding of ligand to AR-positive luminal cells in the prostate epithelium leads to upregulation of growth factors, which diffuse across the basement membrane to affect stromal cells, leading to activation of signaling molecules.³⁷ In the prostate, these signal transduction cascades can lead to stimulation or inhibition of AR transcriptional activity.⁴⁴ Stimulation of AR transcriptional activity can contribute to PCa development by promoting proliferation at low androgen levels. In contrast, inhibition of AR transcriptional activity might contribute to progression by promoting selection of clonal populations that are able to proliferate in an AR-independent manner.⁴⁴

Role of DHT and 5 α -Reductase in PCa

A growing body of evidence has suggested that DHT and 5AR might play important roles in the development and progression of PCa. As described, DHT is regulated by 5AR. This enzyme is overexpressed in PCa relative to BPH.⁴⁵⁻⁴⁷ Compared with the levels in BPH, type 1 5AR is increased in prostatic intraepithelial neoplasia and primary PCa and is further increased in recurrent cancer and PCa metastasis.⁴⁶ Type 2 5AR expression is lower in prostatic intraepithelial neoplasia and primary PCa relative to the levels in BPH, and the levels of type 2 5AR in recurrent cancer and metastases do not differ from those in BPH. Thus, type 2 5AR expression increases with disease expression but is nonetheless not elevated relative to the levels observed in BPH. A recent study by the same group confirmed that type 1 5AR is overexpressed in many PCa cases and demonstrated that the levels of types 1 and 2 5AR expression are increased in localized high-grade PCa compared with low-grade PCa.⁴⁷ As described, the Guevedoce population (Dominican pseudohermaphrodites) have a congenital deficiency of type 2 5AR.³⁰ PCa cases have not been reported in this group of individuals, possibly reflecting a requirement of type 2 5AR for the development of PCa. In Guevedoce, the type 2 5AR deficiency leads to markedly suppressed DHT levels²⁹; therefore, less DHT is available to stimulate the ARs. As described, AR signaling plays an important role in the development and progression of PCa. Together, these observations underscore the importance of DHT and 5AR in the pathophysiology of PCa.

Scientists have hypothesized that inhibition of 5AR in adults might reduce the risk of prostatic disease development, slow or prevent disease progression, and/or treat existing disease.^{37,48,49} The generally protracted course of early PCa provides an important opportunity for early in-

tervention in this disease. The potential targets for blockade of androgen signaling include ARs and 5AR.^{42,50,51} Accordingly, blockade of AR signaling might involve AR inhibitors and 5AR inhibitors (5ARIs). Androgen ablation, achieved by inhibiting luteinizing hormone release and administering AR-blocking agents (eg, flutamide, bicalutamide), is currently considered the mainstay of treatment of PCa.^{48,51} A major drawback of androgen ablation therapy, however, is the development of adverse effects, particularly sterility and impotence, which can result from the inhibition of testosterone synthesis or AR blockade. By inhibiting DHT synthesis, 5ARIs reduce the androgen drive to the prostate while maintaining testosterone levels and thus would not be expected to produce the adverse effects associated with decreased testosterone levels.⁴⁸

5ARIs are under investigation as possible tools for reducing the risk of developing future PCa. Finasteride is a type 2 5ARI, and dutasteride is a dual 5ARI that inhibits both types 1 and 2 5ARs.³⁷ Finasteride was shown to reduce the incidence of PCa events by ~25% in the landmark Prostate Cancer Prevention Trial (PCPT). However, a greater proportion of tumors with a Gleason score of ≥ 7 were found in the finasteride arm of the trial compared with that in the placebo arm.⁵² At least part of this outcome might have been caused by a PSA-driven ascertainment bias, such that PSA had better sensitivity for detecting PCa in the finasteride arm than in the placebo arm, resulting in the greater detection of overall and high-grade PCa.³⁷ Thus, a potential bias might have been present for detecting high-grade disease in smaller glands in the finasteride group relative to the placebo arm. On the basis of finasteride's inhibition of type 2 5AR, it has been theorized that inhibition of both types 1 and 2 5AR could be more effective in preventing PCa because type 1 5AR is overexpressed in localized high-grade cancer relative to its expression in low-grade cancer.^{49,51}

Three Phase III studies that examined the effects of giving dutasteride to a patient population with BPH together found an ~50% decrease in PCa events.⁵³ This preliminary evidence prompted initiation of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which is powered to evaluate the safety and efficacy of dutasteride in reducing PCa events in a population of men at high risk of PCa.⁵⁴ The trial designs of PCPT and REDUCE have been compared comprehensively in another report by Andriole in this Supplement. In brief, some of the main differences in the trial designs were that the PSA level for inclusion was >2.5 ng/mL in the REDUCE trial and was <3.0 ng/mL in the PCPT. The REDUCE trial lowered the minimum age (by 5 years) for inclusion. The REDUCE trial was also specifically designed to recruit men at increased risk of developing PCa. The differences in trial design might increase the chance of showing the effect of dutasteride on the risk of PCa compared with placebo. Whether dutasteride's dual 5AR inhibition reduces the PCa incidence more effectively

than type 2 5AR inhibition alone is of considerable interest, especially in terms of prevention and risk reduction paradigms. Other reports in this Supplement have reviewed the results and design of the PCPT and REDUCE clinical trials and discussed how 5ARIs affect the detection and natural history of PCa in high-risk individuals.

CONCLUSIONS

PCa is a highly prevalent disease that imposes a significant burden on patients and the public healthcare system. The incidence of PCa is expected to increase as the U.S. population continues to age. Black men appear to be disproportionately affected; white men are significantly less likely to develop the disease; and Hispanic and Asian-American men have lower rates than white men. The natural history of PCa is far from completely understood, but our picture of the development and progression of PCa continues to increase as data from a number of ongoing clinical trials accrue. In most patients, early-stage PCa exhibits a relatively nonaggressive course during the first 15 years after diagnosis. Thus, early intervention can operate within a relatively generous window of therapeutic opportunity. Testosterone, the primary androgen in men, is converted to DHT by 5AR. DHT appears to play an important role in the development and maintenance of PCa by way of its interactions with the AR. Studies aimed at elucidating the cellular pathways involved in the development of PCa continue to identify potential therapeutic targets. In the effort to reduce the risk of PCa, the inhibition of 5AR is a valid, and promising, treatment strategy.

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