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REVIEW

Prostate Disease

Differential expression of 5-alpha reductase isozymes in the prostate and its clinical implications

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The development of human benign or malignant prostatic diseases is closely associated with androgens, primarily testosterone (T) and dihydrotestosterone (DHT). T is converted to DHT by 5-alpha reductase (5-AR) isozymes. Differential expression of 5-AR isozymes is observed in both human benign and malignant prostatic tissues. 5-AR inhibitors (5-ARI) are commonly used for the treatment of benign prostatic hyperplasia (BPH) and were once promoted as chemopreventive agents for prostate cancer (PCa). This review discusses the role of the differential expression of 5-AR in the normal development of the human prostate and in the pathogenesis and progression of BPH and PCa.

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INTRODUCTION

The development of human benign or malignant prostatic diseases is androgen-dependent. Testosterone (T), the most abundant androgen in serum, is synthesized and secreted by the testes (95%) and adrenal glands (5%). However, T is not the primary androgen responsible for the development, growth and pathogenesis of the prostate.[1,2] 5-alpha reductase (5-AR) converts T to dihydrotestosterone (DHT), which is the more potent ligand for androgen receptor (AR), and ligand binding to AR leads to an interaction with the androgen response elements of gene promoters.[3] Upon ligand-AR binding and transactivation, the DHT-AR complex translocates into the nucleus and binds to androgen response elements to activate the transcription of AR-regulated genes. DHT-AR binding is more stable than T-AR binding with a three-fold lower dissociation rate[4,5] and is more efficient with a 10-fold higher potency of AR signal transduction.[6] DHT is the most prevalent and potent form of androgen in various human organs and tissues and plays a crucial role in the pathogenesis and progression of several diseases such as benign prostatic hyperplasia (BPH), prostate cancer (PCa), male pattern baldness, hirsutism and acne.[7]

Three types of 5-AR isozymes, 5-AR1, 5-AR2 and 5-AR3, which are encoded by three distinct corresponding genes, *SRD5A1, SRD5A2* and *SRD5A3,* exhibit differential expression patterns in the human body.[8] 5-AR1 is primarily expressed in the skin and liver, while 5-AR2 is mainly found in the seminal vesicles, epididymis and prostate.[9,10] 5-AR3 has recently been detected and described in castrate-resistant PCa.[11] 5-AR plays a critical role in the normal development of the human prostate and in the pathogenesis and progression of prostatic diseases. As an inhibitor of the conversion of T to DHT, 5-AR inhibitors (5-ARIs) are currently used for the prevention and treatment of these conditions.[12] The purpose of this review is to discuss the differential expression of 5-AR isozymes and their role in prostate development and the pathogenesis of prostatic diseases in an effort to define the therapeutic role of 5-ARI.

THE BIOLOGY OF 5-AR ISOZYMES

Characteristics of 5-AR isozymes

The 5-AR family consists of 5-AR1, 5-AR2 and 5-AR3 (**Table 1**). Both 5-AR1 and 5-AR2 are microsomal nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzymes with 259 and 254 amino acid residues and molecular weights of 29.5 and 28.4 kDa, respectively. The pH optimum for 5-AR1 is 6–8.5, while that for 5-AR2 is 5–5.5.[13-15] The newly detected 5-AR3 is also a microsomal NADPH-dependent enzyme made up of 318 amino acid residues.[11,16] The gene architectures of *SRD5A1, SRD5A2* and *SRD5A3* are similar, with five exons and four introns. However, these genes are located on different chromosomes, with *SRD5A1* on 5p15, *SRD5A2* on 2p23 and *SRD5A3* on 4q12.[11,13-16]

Tissue distribution of 5-AR isozymes

Both 5-AR1 and 5-AR2 are expressed throughout human life.[17,18] 5-AR1 is detected at quite low levels in the fetal scalp and nongenital skin, while 5-AR2 is expressed in the external genital skin early in gestation.[9,10,19] In adults, 5-AR1 is expressed in nongenital skin, the liver and certain brain regions, and also at lower levels in the prostate, genital skin, epididymis, seminal vesicles, testis, adrenal gland and kidney. 5-AR2 is expressed at relatively high levels in the prostate, genital skin, epididymis, seminal vesicles and liver.[9,10,13,18,20] Godoy *et al.*[21] examined the expression of 5-AR3 in various benign and malignant tissues and reported that 5-AR3 was overexpressed in lung adenocarcinoma, testicular seminoma and yolk sac tumors, androgen sensitive PCa and castration-recurrent PCa relative to their benign counterparts.

MUTATION OF 5-AR GENES AND HUMAN DISEASE

The significance of 5-AR in human disease was appreciated after the discovery of 5-AR2 deficiency in 1974. The clinical syndrome of 5-AR2 deficiency, male pseudohermaphroditism, was first discovered in the Dominican Republic[22] and the United States of America.[23]

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Subsequently, 5-AR2 deficiency syndrome was reported in many areas throughout the world.[24-27] 5-AR2 deficiency is caused by mutations of the 5-AR2 gene resulting in disorders of sexual development in which 46XY men possess male internal urogenital tracts but female external genitalia. [28] The biochemical features of 5-AR2 deficiency include (**Figure 1**): (a) low normal to low levels of plasma DHT, (b) high normal to elevated levels of plasma T, (c) decreased plasma and urinary 3α-androstanediol glucuronide, a major metabolite of DHT, (d) decreased levels of urinary 5-AR metabolites of C21 and C19 steroids and increased 5-β/5-α reductase urinary metabolite ratios and (e) increased plasma levels of luteinizing hormone.[18,20,29,30] In 5-AR2 deficient men, Thiele *et al.*[31] reported that 5-AR1 may play a critical role in the masculinization of 5-AR2 deficient men. Cantagrel *et al.*[16] reported that patients with mutations in *SRD5A3* exhibited a multisystemic syndrome with psychomotor delay, cerebellar vermis hypoplasia and eye malformation.

EXPRESSION OF 5-AR IN HUMAN PROSTATE TISSUE

The prostate is a ductal-acinar gland, the growth and development of which begins in fetal life and reaches completion at sexual maturity. The prostate initiates its development from the urogenital sinus in the 3rd month of fetal growth and its development is directed primarily by DHT rather than T.[32,33] In the human prostate, both 5-AR1 and 5-AR2 are present in epithelial and stromal cells, while 5-AR2 is the predominant isozyme in stromal cells.[10,13,33] 5-AR3 is expressed by basal epithelial cells.[21]

EXPRESSION OF 5-AR IN BPH AND PROSTATE CANCER

Several studies have characterized the localization of the 5-AR isozymes in BPH and PCa. Habib *et al.*[34] investigated the expression of 5-AR1 and 5-AR2 in BPH by reverse transcription-polymerase chain reaction and *in situ* hybridization. 5-AR1 and 5-AR2 mRNA were found in the glandular areas of BPH, while weaker signals were observed in the stroma. The 5-AR2 expression level was approximately three times that of 5-AR1. Shirakawa *et al.*[35] found that 5-AR1 was predominantly expressed in epithelial cells, while 5-AR2 was expressed in both stromal and epithelial cells. In our experiments,[36] immunostaining with the 5-AR2 antibody showed that 5-AR2 was mostly expressed in epithelial cells with some expression in the stromal compartment. Some BPH tissues (29%) exhibited no or very low 5-AR2 expression. Thomas *et al.*[37] determined the expression of 5-AR1 and 5-AR2 in BPH and PCa by immunohistochemistry and enzyme activity assays. Low to moderate expression of 5-AR1 was observed in the nucleus of BPH cells, while high, primarily cytoplasmic expression of 5-AR1 was frequently observed in PCa. In another study, Thomas *et al.*[38] reported that the expression of 5-AR1 was low in BPH and increased from prostatic intraepithelial neoplasia (PIN) and primary PCa to recurrent and metastatic PCa. In contrast, the expression of 5-AR2 was lower in PIN and PCa than in BPH. In contrast, Titus *et al.*[39] observed high expression of 5-AR1 and 5-AR2 in PCa, with greater expression in high-grade PCa compared with low-grade PCa.[40] Godoy *et al.*[21] reported that the expression of 5-AR3 was restricted to the basal epithelial cells in benign prostate tissue. In high-grade PIN, 5-AR3 was expressed in both basal and neoplastic epithelial cells. Furthermore, in androgen-sensitive and castration-recurrent PCa, 5-AR3 was expressed in the cytoplasm of most epithelial cells.

Overall, both 5-AR1 and 5-AR2 are present in the epithelial and stromal cells of benign prostate tissues, while 5-AR2 is the predominant isozyme in stromal cells. 5-AR3 is expressed by basal epithelial cells. Similarly, in BPH, 5-AR1 is mainly expressed in epithelial cells, while 5-AR2 is expressed in both stromal and epithelial cells. 5-AR3 is expressed in both basal and neoplastic epithelial cells of PIN and in the cytoplasm of epithelial cells in PCa. Both 5-AR1 and 5-AR2 are overexpressed in BPH compared with the normal prostate and 5-AR2 is the predominant form. Decreased expression of 5-AR2 and increased expression of 5-AR1 were observed in PIN and PCa compared with BPH. The differential expression of 5-AR1 and 5-AR2 in prostate cancer implies that dual inhibitors of 5-AR1 and 5-AR2 may be more effective in the prevention and treatment of low-risk PCa.

It is well-known that T is converted to DHT by 5-AR. Several articles have reported the levels of T and DHT in serum and prostate tissue. Olsson *et al.*[41] investigated the local intraprostatic and peripheral serum DHT levels in patients undergoing radical prostatectomy for localized prostate cancer. They found that the local prostatic concentration of DHT was almost twofold higher than in the peripheral serum, with no difference observed between local prostatic and peripheral serum T levels. A positive correlation was observed between local prostatic and peripheral serum DHT levels and between prostate weight and local prostatic DHT levels, but not peripheral serum DHT. The prostate gland is an important source of DHT production as an endocrine organ.

Table 1: Properties of 5-AR isozymes

Properties	*5AR-1*	*5AR-2*	*5AR-3*
Size	259 amino acids	254 amino acids	318 amino acids
Protein	NADPH-dependent	NADPH-dependent	NADPH-dependent
Tissue distribution	Liver, nongenital skin, scalp, sebaceous gland, brain, ovary, prostate, testis	Prostate, epididymis, seminal vesicle, uterus, genital skin, breast, hair follicle, placenta, testis	Brain, liver, prostate, epididymis
Gene name	SRD5A1	SRD5A2	SRD5A3
Gene structure	5 exons, 4 introns	5 exons, 4 introns	5 exons, 4 introns
Chromosome location	5p15	2p23	4q12

5-AR: 5-alpha reductase; NADPH: nicotinamide adenine dinucleotide phosphate. Data for table obtained from reference[9-21]

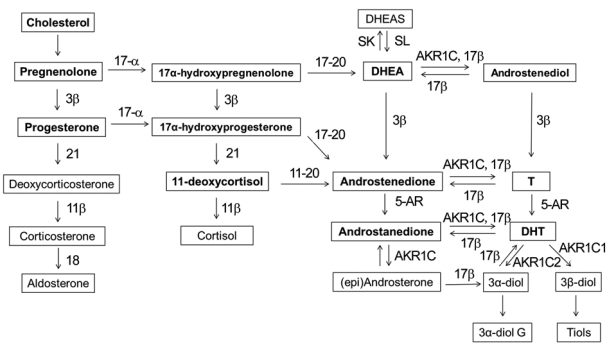

Figure 1: Pathway of steroid biosynthesis and the conversion of T to DHT by 5-AR. C21 precursors (pregnenolone and progesterone) are converted to C19 adrenal androgens (DHEA and androstenedione) by sequential hydroxylase and lyase activities. Circulating adrenal androgens enter the prostate and can be converted to T or androstanedione by a series of reactions involving the activity of 3β and 17β enzymes. T is then converted to the potent androgen DHT by the activity of 5-AR. 17α: 17α-hydroxylase; 17,20: 17,20-lyase; 21: 21-hydroxylase; 3β: 3-HSD (hydroxysteroid dehydrogenase); 17β: 17-HSD (hydroxysteroid dehydrogenase); DHEA: dihydroepiandrosterone; AKR1C: aldo-keto reductase; 3α-diol: 5α-androstane-3α, 17β-diol; 3β-diol: 5α-androstane-3β, 17β-diol.

Androgen metabolism in the prostate not only plays an intracrine role, but more importantly serves as a systemic and locoregional androgen regulator to ensure normal prostate growth, and as such is involved in the pathogenesis of prostatic diseases. In male rats, Kashiwagi *et al*.[42] studied the changes of T and DHT levels in accessory sex organs, serum and seminal fluid after castration. They found that 72 h after castration, T and DHT decreased to 42% and 3% of normal levels in the prostate, respectively, while serum androgen concentrations were below the limit of quantification 6 h after castration and thereafter. The T/DHT ratio in the prostate increased with time over 72 h, while in serum, the T/DHT ratio was initially high but then rapidly decreased within 3 h after castration.

These studies demonstrate that differential expression of 5-AR isozymes is observed in both benign and malignant prostate tissues. Different 5-AR isozymes may play different roles in the development and progression of BPH and PCa. The isozymes' differential expression in benign and malignant human prostate tissues may be relevant when examining the therapeutic effects of 5-ARIs in BPH and PCa. The mechanisms driving the differential expression of 5-AR isozymes have not been studied. In our experiments,[36] we found that methylation of the 5-AR2 promoter region could account for its reduced expression in some adult prostates. We are currently investigating the mechanisms of differential expression of 5-AR1 and 5-AR2 in BPH and PCa.

5-ARIS FOR THE TREATMENT OF BPH

BPH is a pathological condition responsible for considerable morbidity due to urethral obstruction caused by overgrowth.[18] The development of BPH is exclusively dependent on androgens, especially DHT, which is the major intracellular ligand mediating androgen action in prostate cells.[43,44] BPH does not occur in men castrated before puberty.[45] Both 5-AR1 and 5-AR2 are significantly overexpressed in BPH compared with the normal prostate.[46]

5-ARI alone or in combination with an α_1-adrenoreceptor antagonist is the initial treatment option that is currently available for men with BPH. Finasteride, a 4-azasteroid and analogue of T, works by acting as a potent and specific, competitive inhibitor of one of the two subtypes of 5-AR, specifically the 5-AR2 subtype. Dutasteride inhibits two of the three isoforms of 5-AR, 5-AR1 and 5-AR2; whereas, finasteride only inhibits 5-AR2 and has a much shorter half-life. Dutasteride is 45-fold more effective in inhibiting 5-AR1 and two-fold more effective against 5-AR2 than finasteride.[47] Treatment with 5-ARIs for 3 months reduced serum and intraprostatic DHT levels in male rats.[48] For humans, finasteride suppresses DHT by 70.8% ± 18.3% at 24 weeks, while dutasteride results in greater serum DHT suppression with less variability (94.7% ± 3.3% at 24 weeks).[49] The intraprostatic DHT level changes with differential 5-AR isoform expression in different prostatic disease states, and different isoforms have different efficiencies of conversion from T to DHT. Thus, both finasteride and dutasteride are therapeutically effective for BPH patients because 5-AR2 is the predominant form present in BPH. 5-ARI treatment improves clinical symptoms by decreasing prostate size in patients with BPH.[49-52] A number of clinical trials (**Table 2**) demonstrated that the two types of 5-ARIs are effective in treating BPH.[53]

In 1998, 3040 men with urinary symptoms and enlarged prostate glands were enrolled in the Proscar Long-Term Efficacy and Safety Study (PLESS) clinical trial.[54] Patients were randomly assigned into one of two arms, receiving either 5 mg finasteride daily or placebo. Four years later, reduced total prostate volume (TPV), improved symptom scores and increased urinary flow rate were observed in patients in the finasteride arm of the study. Additionally, the effectiveness of finasteride in reducing the risk of acute urinary retention and the need for surgical treatment was demonstrated among men with BPH.

Pooled data from three large ARIA studies (ARIA 3001 in the United States, ARIA 3002 in the United States and ARIA 3003 in 19 countries)[55] verified the efficacy and safety of dutasteride for the treatment of BPH. A total of 4325 men with clinical BPH were enrolled into three trials and treated daily with either 0.5 mg dutasteride or placebo. At 24 months, serum DHT and TPV were reduced by 90.2% and 25.7%, respectively, in the dutasteride group. Dutasteride also reduced the risk of acute urinary retention by 57% and that of BPH-related surgical intervention by 48%. This trial demonstrated that dutasteride was one of the optimal therapeutic options for patients with lower urinary tract symptoms (LUTS) due to BPH.

To compare the effectiveness of finasteride and dutasteride in treating BPH, the Enlarged Prostate International Comparator Study (EPICS)[56] randomized men over the age of 50 to receive 5 mg finasteride ($n = 817$) or 0.5 mg dutasteride ($n = 813$) daily for 12 months. Finasteride and dutasteride treatment were similarly effective in reducing TPV and improving Qmax and LUTS associated with BPH.

In the Medical Therapy of Prostate Symptoms (MTOPS)[57] and Prospective European Doxazosin and Combination Therapy (PREDICT)[58] trials, the efficacy of treatment with finasteride and doxazosin (an α_1-adrenoreceptor antagonist) were studied alone or in combination. In MTOPS, finasteride consistently reduced TPV, both alone and in combination with doxazosin. PREDICT found that the combination therapy was effective in improving urinary symptoms in men with larger (> 40 cm^3) prostates. The combination of Avodart® and Tamslosin (CombAT)[59] study demonstrated that dutasteride alone or in combination with tamsulosin (an α_1-adrenoreceptor antagonist) was more effective in reducing the risk of acute urinary retention or eventual surgery than tamsulosin alone. These 5-ARI trials showed that 5-ARIs, alone or in combination with α_1-adrenoreceptor antagonists, are effective in treating BPH, reducing the risk of acute urinary retention and invasive surgery.

5-ARIS FOR THE PREVENTION AND TREATMENT OF PROSTATE CANCER

PCa is the most commonly diagnosed cancer and is a leading cause of cancer death in men. In 2012, 241 740 new cases of prostate cancer were diagnosed in the US (28.50% of the total of 848 170 new cancer cases in men) with 28 170 deaths (9.33% of the total of 301 170 deaths from cancer for men).[60] Androgens, especially DHT, play key roles in the onset and progression of prostate cancer. 5-ARIs have recently been promoted as chemopreventive or therapeutic agents. A number of clinical trials have been carried out to explore the effects of 5-ARIs (mainly finasteride and dutasteride) for the prevention and treatment of prostate cancer (**Table 3**).

In the Prostate Cancer Prevention Trial (PCPT),[61] 18 882 men with normal digital rectal examinations and prostate-specific antigen (PSA) levels of 3.0 ng ml^{-1} or lower were randomly assigned to daily treatment with either 5 mg finasteride or placebo for 7 years. A prostate biopsy was performed for PSA > 4.0 ng ml^{-1} and/or abnormal digital rectal examination. The primary end-point of this trial was the prevalence of PCa during the study period. PCa was detected in 18.4% of men in the finasteride arm and 24.4% in the placebo arm. High-grade tumors (Gleason grade ≥ 7) were more common in the finasteride arm (6.4%) than the placebo arm (5.1%) ($P < 0.001$). Finasteride reduced the overall incidence of PCa by 24.8%, but the diagnosed cases included more high-grade tumors. To evaluate the risk of high grade cancer upon treatment with finasteride, we established a PC3 and LNCaP grafted

nude mouse model fed with finasteride (100 mg kg^{-1} per day) or placebo for 6 weeks. When prostate cancer cells were grown in combination with mouse fibroblasts or human primary prostate fibroblasts, finasteride activated pro-proliferative signals (p-AKT and p-ERK) and stimulated tumor growth by promoting cell proliferation and repressing cell apoptosis. However, when prostate cancer cells were grown alone or in combination with c-jun-/- fibroblasts, the pro-proliferative function of fibroblasts was repressed. We conclude that fibroblasts and the c-jun expressed inside stromal cells play critical roles in the stromal-epithelial interactions in prostatic tissue. Finasteride upregulates pro-proliferative signals in malignant prostate epithelial cells through its action on stromal cells, consequently stimulating tumor growth by promoting tumor cell proliferation and repressing tumor cell apoptosis. Our findings have significant implications for the use of finasteride as a chemopreventive or therapeutic agent for prostate cancer patients (unpublished data).

To evaluate whether dutasteride reduces the incidence of PCa among men who are at increased risk for the disease, a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial was designed, named the Reduction by Dutasteride of Prostate Cancer Events (REDUCE).[62-64] The enrolled patients met the following criteria: 50–75 years of age, PSA levels of 2.5–10.0 ng ml^{-1} and a negative 6–12 core prostate biopsy within 6 months of enrollment. The participants received a 10-core transrectal ultrasound-guided prostate biopsy at years 2 and 4. PCa was detected in 19.9% of the dutasteride arm compared with 25.1% in the placebo arm, representing an absolute risk reduction of 5.1% ($P < 0.001$) for men given dutasteride. Dutasteride decreased the relative risk of biopsy-detectable PCa by 22.8% (15.2 to 29.8; $P < 0.001$) and this risk reduction was evident across all subgroups tested. However, the absolute incidence of high-grade tumors (Gleason 8–10) was 12 cases in the dutasteride arm, much higher than the one case in the placebo arm; the 4-year difference in the number of Gleason 7–10 tumors between the two arms was not statistically significant.

To assess the effects of dutasteride on the progression of PCa in patients who have failed previous therapies, the Avodart after Radical Therapy for Prostate Cancer Study (ARTS) trial[65,66] enrolled 294 patients who had increasing serum PSA levels after radical prostatectomy or radiotherapy for 2 years. The end-points of this study were time-to-PSA-doubling (PSADT), time-to-disease progression and the proportion of subjects with disease progression. This study showed that dutasteride significantly delayed PSADT and disease progression (which included PSA- and non-PSA-related outcomes) compared with placebo after 20 months of treatment ($P < 0.001$). This study concluded that dutasteride could delay PSA progression in patients with biochemical failure after radical prostatectomy or radiotherapy for PCa.

The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial[67] investigated the safety and

Table 3: Trials of 5-ARIs in the chemoprevention and treatment of prostate cancer

Trial	*PCPT*[56]	*REDUCE*[59]	*ARTS*[60]	*REDEEM*[61]
Publish	2003	2010	2009	2012
Agent	Finasteride	Dutasteride	Dutasteride	Dutasteride
No. of participants	18 882	8231	276	302
Duration	7 years	4 years	2 years	3 years
Age	≥ 55 years	50–75 years	< 85 years	48-82 years
Entry serum PSA	≤ 3.0 ng ml^{-1}	2.5-10 ng ml^{-1}	≥ 0.4 ng ml^{-1} (after RP) ≥ 2 ng ml^{-1} (after RT)	≥ 11 ng ml^{-1}
Rate of incidence or progression	Fi: 18.4%	Du: 19.9%	No data	Du: 38%
	Pl: 24.4%	Pl: 25.1%		Pl: 48%
High grade tumor incidence	Fi: 37.0%	Du: 6.7%	No data	Du: 14%
(Gleason score≥7)	Pl: 22.2%	Pl: 6.8%		Pl: 16%
Overall relative risk reduction in PCa vs placebo	0.248	0.228	No data	No data

5-ARI: 5-alpha reductase inhibitors; ARTS: avodart after radical therapy for prostate cancer study; DU: dutasteride; Fi: finasteride; PCa: prostate cancer; PCPT: prostate cancer prevention trial; Pl: placebo; PSA: prostate-specific antigen; REDEEM: reduction by dutasteride of clinical progression events in expectant management trial; REDUCE: reduction by dutasteride of prostate cancer events trial; RP: radical prostatectomy; RT: radiotherapy

Table 2: Therapeutic trials of 5-ARIs in the treatment of BPH

Trial	*Published*	*Agent*	*Number*	*Duration*	*▲IPSS*	*Qmax (ml s^{-1})*	*▲TPV*
PLESS[50]	1988	Finasteride	3040	4 years	Fi: –3.4	Fi: 1.9	Fi: –18%
						Pl: 0.2	Pl: +14%
ARIA[51]	2002	Dutasteride	4325	2 years	Du: –2.2	Du: 2.2	–0.257
						Pl: 0.6	(relative to Pl)
PREDICT[53]	2003	Finasteride	1095	1 year	Pl: -5.7	Pl: 1.4	
		Doxazosin			Fi: -6.6	Fi: 1.8	No data
					Do: -8.3	Do: 3.6	
					Com: -8.5	Com: 3.8	
MTOPS[52]	2003	Finasteride	3047	4.5 years	Pl: -4.9	Pl: 2.8	Pl: +24%
		Doxazosin			Fi: -5.6	Fi: 3.2	Fi: –19%
					Do: -6.6	Do: 4.0	Do: +24%
					Com: -7.4	Com: 5.1	Com: –19%
CombAT[54]	2010	Dutasteride	4844	4 years	Du: -6.4	Du: 2.0	Du: –28%
		Tamulosin			Ta: -4.9	Ta: 0.7	Ta: +4.6%
					Com: -7.3	Com: 2.4	Com: –27%
EPICS[49]	2011	Finasteride	1630	1 year	Fi: -5.8	Fi: 1.8	Fi: –27.4%
		Dutasteride			Du: -6.2	Du: 2.1	Du: –27.4%

5-ARI: 5-alpha reductase inhibitors; ARIA: ARIA 3001, 3002, 3003; BPH: benign prostatic hyperplasia; Com: comparison; CombAT: the Combination of Avodart® and Tamslosin; DO: doxazosin; DU: dutasteride; EPICS: Enlarged Prostate International Comparator Study; Fi: finasteride; MTOPS: medical therapy of prostate symptoms; PLESS: proscar long-term efficacy and safety study group; PREDICT: prospective european doxazosin and combination therapy; PI: placebo; TA: tamulosin; TPV: total prostate volume; IPSS: the international prostate symptom score

efficacy of dutasteride on PCa progression in men with low-risk disease. In this randomized, double-blind, placebo-controlled trial, participants all had low-risk PCa (TPV < 80 cm^3, PSA ≤ 10 $ng\,ml^{-1}$ and Gleason score ≤ 6). Participants were randomized to receive 0.5 mg dutasteride or placebo daily and were assessed by a prostate biopsy at 18 months and 3 years. PCa progression was observed in 38% of men in the dutasteride arm and 48% in the placebo arm ($P < 0.001$) over 3 years. The REDEEM trial demonstrated that dutasteride can reduce the need for aggressive treatment of low-risk PCa in men under active surveillance.

These studies demonstrated that 5-ARIs (finasteride and dutasteride) can prevent or delay the emergence and progression of PCa, but at the risk of promoting the development of high-grade tumors. Decreased expression of 5-AR2 and increased expression of 5-AR1 were observed in PCa compared with BPH. Therefore, dutasteride, the dual inhibitor of 5-AR1 and 5-AR2, is presumed to be more effective in preventing and treating PCa. The American Society of Clinical Oncology and the American Urological Association have provided clinical practice guidelines for the use of 5-ARIs in PCa chemoprevention.[68] These recommendations state that physicians should inform their patients of the risks and benefits of preventive therapy using 5ARIs.

CONCLUSIONS

Three types of 5-AR isozymes exist in human prostate tissue. Both 5-AR1 and 5-AR2 are overexpressed in BPH compared with normal prostate, and 5-AR2 is the predominant form. Decreased expression of 5-AR2 and increased expression of 5-AR1 were observed in PCa compared with BPH. The differential expression of 5-AR1 and 5-AR2 in prostate cancer implies that dual inhibitors of 5-AR1 and 5-AR2 may be more effective in the prevention and treatment of low-risk PCa. More work is necessary to identify the expression and function of 5-AR3 in the prostate and to understand the mechanism of differential expression of 5-AR isozymes in the prostate. Clinical trials, such as REDEEM, have reported that dutasteride delayed the progression of low-risk PCa. More mechanistic investigations are needed to understand the effects of 5-ARIs fully.

AUTHOR CONTRIBUTIONS

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections. KW substantially contributed to the design, preparation, drafting and revising of the final version of the manuscript under the supervision of YNN. YNN also provided extremely important intellectual support, made critical revision of the manuscript for important intellectual content and obtained funding. DDF, SJ and NZX substantially contributed to the preparation, drafting and revising of the final version of the manuscript and all the authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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