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Review

The role of CYP17A1 in prostate cancer development: structure, function, mechanism of action, genetic variations and its inhibition

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Abstract. Androgens play an important role during the development of both normal prostate epithelium and prostate cancer and variants of genes involved in androgen metabolism may be related to an increased risk of prostate disease. Cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1) is a key regulatory enzyme in the steroidogenic pathway; it catalyses both 17α-hydroxylase and 17,20-lyase activities and is essential for the production of both androgens and glucocorticoids. In this review, we focus on the structure and enzymatic activity of CYP17A1 and the mechanism of modulation of CYP17A1 activities. We discuss the relationship between common genetic variations in *CYP17A1* gene and prostate cancer risk and the main effects of these variations on the prediction of susceptibility and clinical outcomes of prostate cancer patients. The mechanism of action, the efficacy and the clinical potential of CYP17A1 inhibitors in prostate cancer are also summarized.

Key words: CYP17A1 — Steroid 17 alpha-hydroxylase/17,20-lyase — *CYP17A1* polymorphisms — CYP17A1 inhibitors — Prostate cancer

Abbreviations: AA, abiraterone acetate; ACTH, adrenocorticotropic hormone; ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; CYP17A1, cytochrome P450 17α-hydroxylase/17,20-lyase; DHEA, dehydroepiandrosterone; GWAS, genome-wide association studies; KLK2, kallikrein-related peptidase 2; KLK3, kallikrein-related peptidase 3; mLTC-1 cells, murine primary Leydig cells; P-450-red, NADPH-cytochrome P450 reductase; PCa, prostate cancer; PSA, prostate-specific antigen; SF-1, steroidogenic factor-1; SLC45A3, prostein; SNPs, single nucleotide polymorphisms; TNM, tumour-node-metastasis stage; UTR, untranslated region.

Introduction

Prostate cancer (PCa) is the second most common cancer-related cause of death in men worldwide and is caused in its aetiology by numerous genetic and environmental factors (Nelson and Lepor 2003). It is estimated that 161,360 new PCa cases will be diagnosed and that 26,730 deaths will occur in the United States in 2017 (Siegel et al. 2017). Epidemiological data demonstrate that the incidence and mortality rate of PCa varies in different countries and regions and, hence, the influence of racial or ethnic differences varies (DeSantis et al. 2016; Torre et al. 2016; Siegel et al. 2017). With early diagnosis, radical prostatectomy and/or radiation therapy are potentially curative. For advanced or metastatic PCa, hormonal therapies, reducing androgen levels by surgical or chemical castration or by inhibiting the androgen receptor protein, are employed (Rove et al. 2012; Zhuang and Johnson 2016). Despite technological advancements, the management of PCa has become progressively more complex and controversial for both early and late-stage disease. The limitations and potential harm associated with the use of prostate-specific antigen (PSA) as a diagnostic marker have stimulated significant investigation of numerous novel biomarkers that demonstrate various capacities to detect PCa

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and that can decrease unnecessary biopsies (Cabarkapa et al. 2016; Sharma et al. 2017).

Genetic alterations in the testosterone metabolism pathway are expected to alter hormonal homeostasis and probably influence PCa development and progression (Henríquez-Hernández et al. 2015). Several genes have been identified as risk factors contributing to PCa. One of them is the gene for cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1), a pivotal enzyme for androgen synthesis. CYP17A1 catalysis leads to either steroid precursors of glucocorticoids (e.g. cortisol) that regulate immune response or androgens (e.g. testosterone) that drive the development and maintenance of male characteristics or are converted to oestrogens in females (Auchus and Miller 1999; Pandey and Miller 2005; Yoshimoto and Auchus 2015). Mutations in *CYP17A1* gene cause 17α-hydroxylase deficiency, a rare form of congenital adrenal hyperplasia, and sexual infantilism (Costa-Santos et al. 2004). The discovery that the *CYP17A1* gene is polymorphic has prompted the investigation of the role of gene variants in the aetiology of diseases and conditions in which oestrogens or androgens play an important role, notably breast cancer, polycystic ovary syndrome, endometrial cancer and PCa (Sharp et al. 2004).

This review aims to summarize the recent gains in our comprehension of the role of CYP17A1 in PCa and of the mechanisms regulating and modifying its activity. We explore the influence of *CYP17A1* gene polymorphisms in PCa development and progression and the effects of established CYP17A1 inhibitors, such as ketoconazole, abiraterone acetate, galeterone and VT-464, which are agents currently at various stages of development.

CYP17A1 structure, function and mechanism of action

CYP17A1 (EC 1.14.99.9) is a membrane-bound dual-function monooxygenase that possesses 17α-hydroxylase and 17,20-lyase activities. According to the structural model of CYP17A1, it is composed of 508 amino acids, with 4 important structural domains, including a substrate-binding domain, a catalytic activity area, a haem-binding region and a redox-partner binding site (Auchus and Miller 1999; Auchus 2001). It is localized to the endoplasmic reticulum in the adrenal glands, testicular Leydig cells and ovarian thecal cells and lies at the crossroads of sex steroid and glucocorticoid synthesis (Missaghian et al. 2009). Human

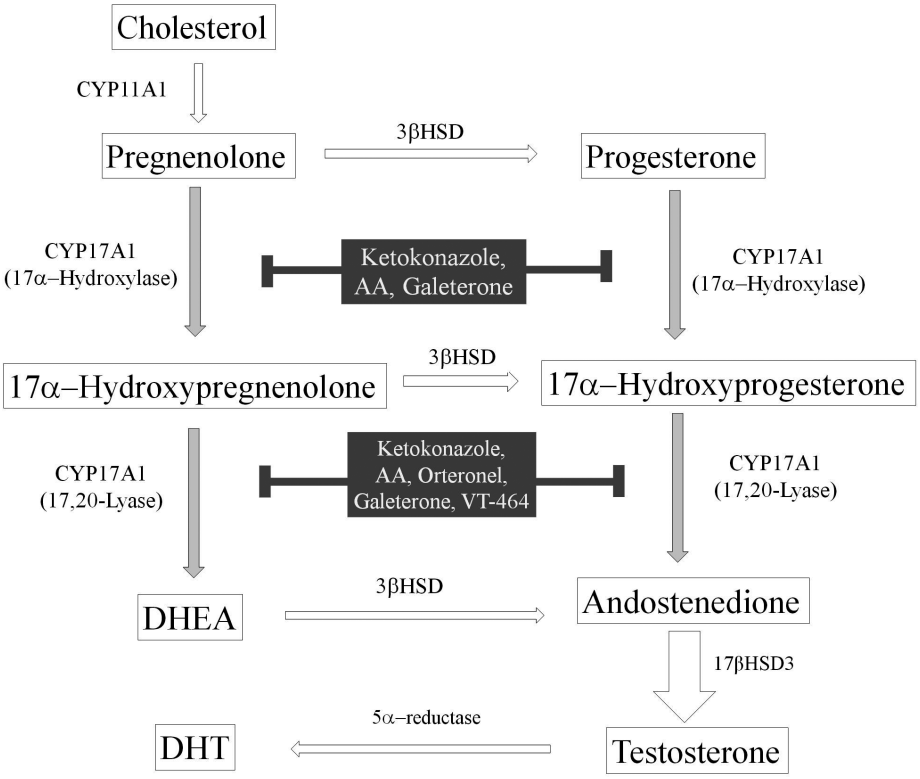

Figure 1. Testosterone synthesis and enzymatic activity of CYP17A1. Inhibitors of CYP17A1 in the pathway are also indicated. Androgen synthesis requires two key cytochrome P450 enzymes (CYP11A1 and CYP17A1) and two hydroxysteroid dehydrogenases (3βHSD and 17βHSD). CYP17A1 catalyzes two essential reactions in androgen biosynthesis. The first one is the conversion of pregnenolone to 17α-hydroxypregnenolone and progesterone to 17α-hydroxyprogesterone through its 17α-hydroxylase activity. The second reaction in androgen biosynthesis is conversion of 17α-hydroxypregnenolone to DHEA and 17α-hydroxyprogesterone to androstenedione through its 17,20-lyase activity. Ketoconazole is a weak and nonspecific CYP17A1 inhibitor. AA inhibits both the 17α-hydroxylase and 17,20-lyase activity of CYP17A1. Orteronel and galeterone have increased specificity for 17,20-lyase relative to 17α-hydroxylase. VT-464 has higher specificity for the 17,20-lyase reaction over 17α-hydroxylase. AA, abiraterone acetate; 3βHSD, 3β-hydroxysteroid dehydrogenase; 17βHSD3, 17β-hydroxysteroid dehydrogenase 3; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.

CYP17A1 is known to catalyse at least 13 different reactions with endogenous substrate and even some minor activities are physiologically important (Yoshimoto and Auchus 2015). The 17α-hydroxylase activity of CYP17A1 is required for the hydroxylation of pregnenolone and progesterone at the C_{17} position to generate 17α-hydroxypregnenolone and 17α-hydroxyprogesterone. Its second enzymatic activity follows with the cleavage of the C_{17}-C_{20} bond of either 17α-hydroxypregnenolone or 17α-hydroxyprogesterone to form dehydroepiandrosterone (DHEA) and andostenedione, respectively (Fig. 1) (Auchus 2001; Pandey and Miller 2005; Yoshimoto and Auchus 2015). In human adrenal steroidogenesis, CYP17A1 is the qualitative regulator that determines the class of steroids synthesized in various cell types: in its absence, mineralocorticoids are produced; if only its 17α-hydroxylase activity is present, glucocorticoids are produced; if both its 17α-hydroxylase and 17,20-lyase activities are present, precursors of sex steroids are produced (Pandey and Miller 2005; Yoshimoto and Auchus 2015).

The reaction mechanism for each activity is thought to involve the formation of distinct iron–oxygen complexes. For the hydroxylation mechanism, the oxo-intermediate, Fe^{V}=O, is considered to be the active catalytic oxygen-bound CYP17A1 complex (Atkinson and Ingold 1993). Possible candidates for the acyl-carbon bond cleavage have been suggested, namely both the iron-peroxo, Fe^{III}-OOH, and iron-oxo, Fe^{V}=O species (Lee-Robichaud et al. 1995; Akhtar et al. 2005).

Previous observations have shown that the following factors contribute to the regulation of the ratio of 17,20-lyase activity to 17 α-hydroxylase activity: (a) the input of two electrons from NADPH of NADPH-cytochrome P450 reductase (P-450-red) to CYP17A1 (Auchus and Miller 1999). (b) The presence of cytochrome b_5. Two general mechanisms have been proposed to explain the enhanced action of cytochrome b_5 in CYP17A1 catalysis. The first mechanism implies that, during the reductive stages of CYP17A1, the second electron for the completion of the catalytic cycle can be derived from cytochrome b_5, an alternative redox partner to the conventional P-450-red (Estabrook 1999). A second model suggests that cytochrome b_5 serves as an allosteric modulator that can increase 17,20-lyase activity by acting as an allosteric effector on the CYP17A1–P450-red complex, facilitating electron transfer from P450-red to CYP17A1 or promoting the facile breakdown of the CYP17A1-substrate intermediate in the catalytic cycle (Storbeck et al. 2013). (c) Phosphorylation of the serine/threonine residues of the CYP17A1 protein increases 17,20-lyase activity but does not affect 17α-hydroxylase activity (Zhang et al. 1995; Biason-Lauber et al. 1997; Miller and Tee 2015). The activities of CYP17A1 have been hypothesized to be differentially regulated by protein phosphorylation based on the differential expression of protein kinases and/or phosphatases in various cell types or at various times during in development, thus determining the pattern of steroid hormones produced (Pandey and Miller 2005).

Notably, CYP17A1 has been shown to have additional properties, namely by metabolizing xenobiotics and catalysing the formation of a third class of active steroids, the 16-ene steroids. However, the overall functional effect of the 16-ene steroids in normal physiology is still poorly understood (Vasaitis et al. 2011).

CYP17A1 gene

The human *CYP17A1* gene is localized to chromosome10q24.3, spans 6.6 kb and contains eight exons and seven introns (Picado-Leonard and Miller 1987). An identical 2.1 kb mRNA is transcribed from this gene in the both the adrenals and the gonads (Chung et al. 1987; Fan at al. 1992; Auchus 2017). The expression level of *CYP17A1* is regulated by adrenocorticotropic hormone (ACTH) in the adrenals and by gonadotropic hormone in the testes and ovaries (Yanase et al. 1991; Porubek 2013). The expression of *CYP17A1* mRNA has been shown to be absolutely dependent on cAMP stimulation. Initial studies with reporter gene constructs to define ACTH-dependent transcription of the human *CYP17A1* gene have revealed that both basal and cAMP-responsive elements lie within the first upstream 63 bp of the *CYP17A1* promoter and that a second basal element lies between -184 and -206 bp in the *CYP17A1* promoter (Rodriguez et al. 1997). Subsequently, Sewer and co-workers have shown that the binding of transcription factor steroidogenic factor-1 (SF-1) to this region and its dephosphorylation play an integral role for ACTH/cAMP-mediated steroidogenic *CYP17A1* gene expression (Sewer and Waterman 2002; Sewer et al. 2002).

Several other transcription factors regulate *CYP17A1* gene expression, cell differentiation, and tumorigenesis in diverse cell types, including the gonads and adrenals (Lin et al 2001; Gilep et al. 2011). The ability of these factors to increase *CYP17A1* mRNA expression requires the formation of higher order coregulatory complexes, many of which contain enzymatic activities that post-translationally modify both the transcription factors and histones (Sewer and Jagarlapudi 2009). One of these is the GATA family of transcription factors. GATA1–3 are primarily involved in haematological development, whereas GATA4 and GATA6 have been implicated in human *CYP17A1* expression. GATA6 is highly expressed in the adrenal cortex and the stimulatory actions of GATA6 on *CYP17A1* transcription are independent of DNA binding but occur through the interaction of GATA6 with specificity protein 1 (Sp1) (Kiiveri et al. 2004; Sewer and Jagarlapudi 2009).

GATA4 plays a role in the differentiation and/or steroidogenic function of gonadal somatic cells, including fetal and

adult Leydig cells (Viger et al. 1998; Ketola et al. 1999, 2002). The silencing of GATA4 in mLTC-1 cells (murine primary Leydig cells) and primary adult Leydig cells has been shown to lead to the decreased expression of genes in the androgen biosynthetic pathway including *CYP17A1*. In mLTC-1 cells, this is accompanied by the reduced production of sex steroid precursors (Schrade et al. 2015). Adrenal transcription of the *CYP17A1* gene is also controlled by transcription factors Sp1 and Sp3 (binding to the -127/-184 bp site) and nuclear factor NF-1C proteins (binding to the -107/-185 bp or the -178/-152 bp sites) (Lin et al. 2001). Another transcription factor that regulates the expression of the human *CYP17A1* gene is SET (also known as TAF-1β, I2PP2A and INHAT). It is an evolutionarily conserved transcription factor that participates in the early ontogenesis of the gonadal system, that regulates *CYP17A1* gene transcription in Leydig cells, and that might also activate other genes expressed in immature oocytes, thus playing a role in oocyte development (Xu et al. 2013).

Moreover, epigenetics provides an additional layer of gene regulation through DNA methylation and histone tail modifications. Initial studies of CpG methylation came from studies of bovine and rodent adrenals (Hornsby et al. 1992). Missaghian et al. (2009) have shown that, in rodent adrenals, methylation of the *CYP17A1* promoter region is correlated with the silencing of gene expression and the production of corticosterone as the main glucocorticoid. The absence of a CpG island in the human *CYP17A1* gene suggests that the direct epigenetic regulation of the *CYP17A1* promoter is more essential in rodents and, therefore, that the expression of *CYP17A1* in humans is driven by the above-mentioned complex interaction of transcription factors (Martinez-Arguelles and Papadopoulos 2010).

CYP17A1 gene polymorphisms

Single nucleotide polymorphisms (SNPs) are the most common form of human genetic polymorphisms that can contribute to an individual's susceptibility and progression to cancer. Although many factors can contribute to the underlying biology and clinical course of PCa, genetic variation in androgen biosynthesis is thought most likely to influence the eventual outcome of the disease (Sissung et al. 2014).

CYP17A1 rs743572 gene polymorphism

Genetic variation in *CYP17A1* has been studied extensively in relation to PCa. Most of these studies have focused on rs743572 gene polymorphism (denoted T34C or A1/A2), located 34 bp upstream from the initiation of translation and downstream from the transcription start site (Fig. 2). The variant creates a recognition site for the *Msp*AI restriction enzyme (Sharp et al. 2004). Studies that have reported a relationship between *CYP17A1* gene polymorphism and the risk of PCa have been contradictory in terms of which allele is associated with the increased risk for PCa. Some case-control studies have reported an elevated risk for PCa being related to the *A1/A2* or *A2/A2* genotype (Lunn et al 1999; Gsur et al. 2000; Haiman et al. 2001; Kittles et al. 2001; Yamada et al. 2001; Sobti et al. 2008; Souiden et al. 2011), whereas other studies indicate an association between PCa and the *A1/A1* genotype (Wadelius et al. 1999; Habuchi et al. 2000). Further studies have reported no difference in the distribution of the various alleles among healthy controls and PCa patients (Chang et al. 2001; Latil et al. 2001; Standford et al. 2002; dos Santos et al. 2002; Madigan et al 2003; Hamada et al. 2007; Sivonova et al. 2012; Cai et al. 2012; Karimpur-Zahmatkesh et al. 2013; Ersekerci et al. 2015; Han et al. 2015; Henríquez-Hernández et al. 2015).

Differences also exist in the association between the rs743572 polymorphism and PCa risk in different ethnicities. Meta-analyses have suggested that variants within *CYP17A1* play a role in susceptibility to PCa among African-Americans but not in Caucasian or Asian populations (Ntais et al. 2003; Wang et al. 2011; Taioli et al. 2013; Wang et al. 2015). The reasons for the large ethnic differences might be explain by the observation that African-Americans experience earlier puberty, higher serum levels of total testosterone and a higher incidence of PCa (Loukola et al. 2004). Most recently, Brureau et al. (2016) have found that the *A2* allele and the *A2/A2* genotype are not associated with a significant risk of PCa in two different populations of African ancestry, namely an Afro-Caribbean population from the French West Indies and a native African population from the Democratic Republic of Congo.

The *A2* allele is thought to enhance promoter activity (through creating an additional Sp1-binding site – CCACC

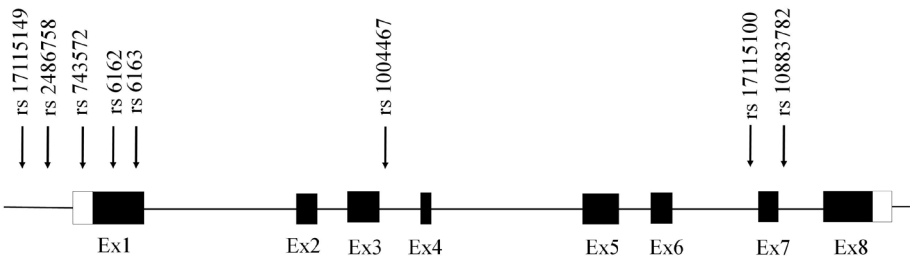

Figure 2. Human *CYP17A1* gene with designated SNPs. Black blocks mark coding exons (Ex1-8), white blocks mark 5′ and 3′ UTRs, and connecting lines between blocks are introns.

box) resulting in an increased rate of transcription and, thus, an increased production of androgens and oestrogens that might affect PCa risk (Stanford et al. 2002). A few studies have shown an association of the *A2* allele with higher levels of plasma testosterone (Zmuda et al. 2001; Kakinuma et al. 2004) but this observation is again contradictory (Lunn et al. 1999; Allen et al. 2001; Haiman et al. 2001).

Similarly no consistent results have been observed relating age, clinical variables (Gleason pathological grade, tumour-node-metastasis (TNM) stage, serum PSA levels and serum levels of sex hormones) and family history with rs743572. A few epidemiologic studies have determined a positive association between this polymorphism and the Gleason score/clinical stage and serum PSA levels (Sobti et al. 2006, 2008) but many more conclusions are negative (Haiman et al. 2001; Stanford et al. 2002; Madigan et al. 2003; Mononem et al. 2006; Okugi et al. 2006; Hamada et al. 2007; Wright et al. 2010; Risio et al. 2011; Souiden et al. 2011; Sivonova et al. 2012; Yamada et al. 2013; Han et al. 2015; Henríquez-Hernández et al. 2015; Brureau et al. 2016; Song et al. 2016). Some of the studies suggest that the *CYP17A1* gene is a risk factor for PCa in males of advanced age (Souiden et al. 2011; Song et al. 2016). Hamada et al. (2007) have reported that the *CYP17A1* polymorphism is a potential prognostic predictor for survival in patients with androgen-independent disease, because patients who carry the *CYP17A1* variant *A2* allele have a longer survival time than patients who do not carry this variant.

Other *CYP17A1* gene polymorphisms

To date, several other *CYP17A1* gene polymorphisms in various gene locations (in the intron regions, in the promoter region, in the coding regions of the exon and in the 5' untranslated region (UTR) region of the exon) have been studied, mainly together with rs743572 (Fig. 2). A family-based study of Loukola et al. (2004) has found no association between 14 SNPs in *CYP17A1* and PCa in a total case-control sample of 1117 brothers from 506 sibships. A family-based study by Douglas et al. (2005) has shown a 2-fold increased risk of PCa in individuals with the common SNP rs619824. Modest but significant positive associations were observed between PCa and two SNPs (rs2486758 and rs6892); this seemed to be stronger among aggressive PCa. Moreover, the variant allele for rs2486758 SNP was found to be associated with a 7% increase in PCa risk (Setiavan et al. 2007). A contemporary study by Lindström et al. (2006) showed that carriers of one allele of the rs2486758 SNP located in the promoter region of *CYP17A1* were at a 15% higher risk of developing PCa.

Yamada et al. (2013) observed significant association of the rs6162, rs6163 and rs1004467 *CYP17A1* polymorphisms with the risk of progression to castration-resistant PCa (CRPC) after initial hormonal therapy for PCa in the Japanese population. They also assumed that rs6162 and rs6163 exhibited their functions in coordination with rs743572 as a haplotype. An association was also seen between genotypes and haplotype distributions of patients and a control group in the Korean population in the analysis of Han et al. (2015). They found that haplotype-2 of *CYP17A1* was significantly associated with PCa susceptibility, whereas rs17115149 and haplotype-4 of *CYP17A1* showed a significant association with the histological aggressiveness associated with Gleason scores.

Significant associations have also been seen between the rs6162, rs6163 and rs743572 genotypes and PCa status in African-American men. Interestingly, Sarma et al. (2008) have observed a strongly decreased risk for PCa in heterozygotes for these three *CYP17A1* SNPs. Another large study has evaluated the association of eight genetic variants of *CYP17A1* in 2,452 samples (886 cases and 1,566 controls) of non-Hispanic Caucasian, Hispanic Caucasian or African-American origin. In African-Americans, the association with PCa risk remained significant for rs104467 and rs17115144 and, in non-Hispanic Caucasians, a significant increase in risk for PCa has been reported for rs10883782 (Beuten et al. 2009).

The relationship was studied between three *CYP17A1* SNPs (rs10883783, rs17115100 and rs743572) and PCa-specific survival and progression outcomes. No genetic association with disease progression was identified. However, men with the variant *A* allele in rs10883783 had a 56% risk reduction in PCa-specific survival (Wright et al. 2010).

GWAS

Although the use of genome-wide association studies (GWAS), next-generation sequencing, whole-exome sequencing and RNA sequencing has allowed the comprehensive analysis of PCa genomes, it has also given an indication of the complexity and heterogeneous nature of PCa (Sissung et al. 2014). GWAS have emerged as a new approach for identifying less penetrant cancer susceptibility alleles that might be associated with the initiation and progression of cancer.

GWAS of PCa have identified approximately 100 different SNPs associated with PCa risk in various racial populations (Gudmundsson et al. 2009; Schumacher et al. 2011; Eeles et al. 2013; Al Olama et al. 2014; Dluzniewski et al. 2015; Hoffmann et al. 2015; Panagiotou et al. 2015; Kim et al. 2016; Hofmann et al. 2017). In some of the GWAS, attempts have been made to evaluate the associations between specific PCa risk SNPs, disease aggressiveness and survival (Schumacher et al. 2011; Al Olama et al. 2014; Berndt et al. 2015; Szulkin et al. 2015). The large GWAS of PSA by Hoffman et

al. (2017) in 28,503 Kaiser Permanente whites and 17,428 men from replication cohorts detected 40 independent SNPs associated with PSA levels: seven common independent SNPs at kallikrein-related peptidase-3 and kallikrein-related peptidase 2 (KLK3-KLK2), five SNPs in or near SLC45A3 (prostein) and a novel SNPs associated with PSA levels in genes in pathways involved in cellular signalling, growth and differentiation. Additionally, results from other GWAS and linkage analyses have reported risk loci associated with aggressive disease among familial cases (Gudmundsson et al. 2008; Liu et al. 2011; Nam et al. 2011; Teerlink et al. 2016). Thus, GWAS are a part of multi-omic approaches (including proteomics, metabolomics and epigenomics) in pursuit of precision medicine and provide opportunities to gain new perspectives regarding the genetic architecture of PCa by identifying new candidate genes and targets.

CYP17A1 inhibitors

More than half century ago, Huggins and Hodges provided clinical evidence that prostate morphogenesis occurs under the control of androgens and is modulated by oestrogens (Huggins et al. 1941). Nowadays, androgen and its androgen receptor (AR) are accepted to be key factors for the development of not only normal prostate, but also PCa (Heinlein and Chang 2004; Fujimoto 2016). This explains the high response rate of PCa patients to androgen deprivation therapy (ADT). However, after an initial response to ADT, most patients experience cancer progression to metastatic CRPC, which is defined by rising PSA and/or clinical progression despite systemic androgen depletion (Damber and Aus 2008; Chang et al. 2014; Attard et al. 2016). CRPC occurs because of the reactivation of the androgen axis either by adaptive intratumoral androgen biosynthesis (Locke et al. 2008; Cai et al. 2011) or by changes in the AR (e.g. AR gene amplification and mutation) (Taplin et al. 1999; Shi et al. 2002).

Therapeutic CYP17A1 inhibition for the treatment of PCa and other androgen-dependent diseases has been envisioned for over 50 years (Fig. 3; Arth et al. 1971). Generally, CYP17A1 inhibitors have been structurally categorized as steroidal or non-steroidal. The steroidal inhibitors are similar in structure to the natural substrates of CYP17A1, pregnenolone or progesterone and often involve the modification of the substrate's D-ring at the C17 position (Vasaitis et al. 2011). An early developed compound, ketoconazole, is an antifungal with weak and nonspecific CYP17A1 inhibitory properties and has been extensively used for the 'off-label' treatment of advanced CRPC (Fig. 1; Yap et al. 2008). It has typically been used at high dosage (800–1200 mg/d) for PCa

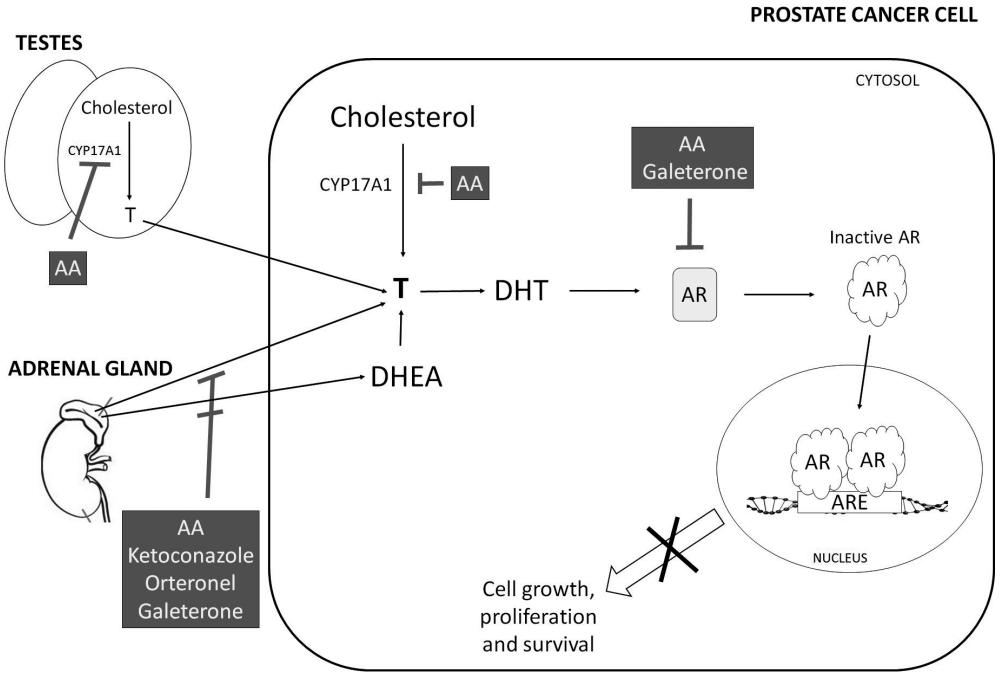

Figure 3. Schematic view of the CYP17A1 inhibitors targeting the androgen receptor signalling pathway. The biological action of androgens is mediated through the AR. In prostate tissue, DHT is the primary ligand for the AR and is synthesized from T by 5α-reductase. Androgen binding to the AR induces conformational changes in the AR leading to dimerization and dissociation from nuclear chaperones, with subsequent translocation of the AR into the nucleus. Nuclear AR binds to androgen responsive elements (AREs) in the DNA with resultant transcriptional activity inducing cellular proliferation. The CYP17A1 inhibitors with a steroidal structure display antiandrogenic effects by inhibiting the intracellular biosynthesis of androgens (T, DHT, DHEA) in the testes, adrenals and prostate cancer cells from cholesterol. In addition to affecting androgen synthesis, some CYP17A1 inhibitors are also able to directly bind to AR and block its activity as a ligand-dependent transcription factor. AA, abiraterone acetate; AR, androgen receptor; ARE, androgen response element; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; T, testosterone.

treatment, lowering not only testosterone levels, but also the levels of adrenal steroids, androstenedione and DHEA (De Coster et al. 1996). However, high doses of ketoconazole have been associated with significant potential side-effects including hepatotoxicity, gastrointestinal toxicity and adrenal insufficiency (Vasaitis et al. 2011). Ketoconazole leads to a decrease in serum PSA by ≥ 50% in 27% of patients, whereas anti-androgen withdrawal causes a PSA response in 11% of patients (Small et al. 2004).

By 2011, the United States Food and Drug Administration (FDA) had approved abiraterone acetate (AA), the first specific inhibitor of CYP17A1 (Fig. 1). AA and its metabolite, abiraterone, are selective inhibitors of 17α-hydroxylase and 17,20-lyase (Vasaitis et al. 2011). Recently, a more active form of AA, namely Δ^4 abiraterone, has been shown to block 17β-hydroxysteroid dehydrogenase and steroid 5α reductase, which are required for dihydrotestosterone synthesis, in addition to CYP17A1 enzymes (Li et al. 2015). It induces PSA declines of ³ 50% in 29–62% of patients, achieves overall survival benefits in both docetaxel refractory and chemotherapy-naıve patients, delays and reduces skeletal-related events and palliates pain (Ryan et al. 2013). In the COU-AA-301 and COU-AA-302 registration trials, abiraterone demonstrated overall survival benefits in post-docetaxel and pre-docetaxel settings (Lorente et al. 2015; Fizazi et al. 2016). The suppression of 17α-hydroxylase leads to reduced cortisol synthesis and compensatory overproduction of mineralocorticoids. Increased mineralocorticoid levels result in some adverse events, such as hypokalaemia, fluid retention, hypertension and cardiac disorders; however, these toxicities are largely abrogated by the co-administration of low-dose glucocorticoids (Attrard et al. 2009). Abiraterone is currently approved in combination with prednisone for the treatment of metastatic CRPC in men both prior to and after treatment with docetaxel (de Bono et al. 2011; Ryan et al. 2013). Although abiraterone represents a significant therapeutic advance, tumours ultimately become resistant and progress. Furthermore, abiraterone-resistant tumours are also frequently resistant to subsequent treatment with enzalutamide, a recently developed AR antagonist that otherwise confers a survival benefit that is similar to that of abiraterone for CRPC (Brasso et al. 2015).

One additional drug with abiraterone-like properties is orteronel (TAK-700) (Fig. 1). It is a nonsteroidal selective inhibitor of 17,20-lyase. In preclinical studies, orteronel more potently inhibited 17,20-lyase relative to 17α-hydroxylase, up to 5.4-fold, with minimal effect on other CYP drug-metabolizing enzymes (Yamaoka et al. 2012). Preliminary results from phase I/II studies found a 63% PSA response rate at 12 weeks with patients given 300 mg twice daily (Zhu and Garcia 2013). More selective specificity of orteronel inhibition leads to less inhibition of 17α-hydroxylase with a reduction in the risk of overproduction of mineralocorticoids. Thus, orteronel is potentially an attractive drug for longer duration therapy or when prolonged corticosteroid is not ideal. However, in a clinical setting, many trials have included prednisone coadministration (Zhu and Garcia 2013; Alex et al. 2016).

Galeterone (VN/124-1, TOK-001) is a CYP17A1 inhibitor with multiple mechanisms of action, including CYP17A1 inhibition, AR antagonism and a decrease in intratumoral AR levels (Fig. 1 and 3; Alex 2016). Additionally, galeterone has a unique mechanism of action by disrupting AR signaling *via* a proteosomal-dependent pathway, leading to AR degradation (Kwegyir-Afful et al. 2015). In a phase I study of chemonaive men with CRPC, 22% demonstrated a decrease in PSA of more than 50%, whereas an additional 26% had a PSA decline of 30–50% after 12 weeks. No evidence of adrenal mineralocorticoid excess was noted (Montgomery et al. 2016).

Finally, an additional drug, namely seviteronel (VT-464, Viamet Pharmaceuticals), is in early stages of development (Fig. 1). It is a novel nonsteroidal CYP17A1 inhibitor and AR antagonist. It preferentially inhibits 17,20-lyase over 17α-hydroxylase, thus offering an advantage over AA from the perspective of not requiring concomitant therapy with prednisone, because of to its minimal effects on upstream steroid levels (Suzman and Antonarakis 2014).

Conclusions

This review summarises the role of CYP17A1 in the synthesis of androgens and the influence of *CYP17A1* SNPs on the susceptibility to the risk of PCa. We also discuss potential new therapeutic strategies that may lead to improvements in the oncological outcomes of this disease. In the future, advances in new technologies with clinical information will offer the possibility of the earlier detection of PCa pathology and will lead to different or specific treatments that will prolong patient survival, delay symptom progression and maintain, if not improve, quality of life.

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References

Akhtar M. K., Kelly S. L., Kaderbhai M. A. (2005): Cytochrome b(5) modulation of 17{alpha}hydroxylase and 17-20 lyase (CYP17) activities in steroidogenesis. J. Endocrinol. **187,** 267–274

https://doi.org/10.1677/joe.1.06375
Al Olama A. A., Kote-Jarai Z., Berndt S. I., Conti D. V., Schumacher F., Han Y., Benlloch S., Hazelett D. J., Wang Z., Saunders E. et al. (2014): A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nat. Genet. **46,** 1103–1109
https://doi.org/10.1038/ng.3094
Alex A. B., Pal S. K., Agarwal N. (2016): CYP17 inhibitors in prostate cancer: latest evidence and clinical potential. Ther. Adv. Med. Oncol. **8,** 267–275
https://doi.org/10.1177/1758834016642370
Allen N. E., Forrest M. S., Key T. J. (2001): The association between polymorphisms in the CYP17 and 5alpha-reductase (SRD5A2) genes and serum androgen concentrations in men. Cancer Epidemiol. Biomarkers Prev. **10,** 185–189
Arth G. E., Patchett A. A., Jefopoulus T., Bugianesi R. L., Peterson L. H., Ham E. A., Kuehl F. A. Jr., Brink N. G. (1971): Steroidal androgen biosynthesis inhibitors. J. Med. Chem. **14,** 675–679
https://doi.org/10.1021/jm00290a003
Atkinson J. K., Ingold K. U. (1993): Cytochrome P450 hydroxylation of hydrocarbons: variation in the rate of oxygen rebound using cyclopropyl radical clocks including two new ultrafast probes. Biochemistry **32,** 9209–9214
https://doi.org/10.1021/bi00086a028
Attard G., Parker C., Eeles R. A., Schroder F., Tomlins S. A., Tannock I., Drake C. G., de Bono J. S. (2016): Prostate cancer. Lancet **387,** 70–82
https://doi.org/10.1016/S0140-6736(14)61947-4
Attard G., Reid A. H., Olmos D., de Bono J. S. (2009): Antitumor activity with CYP17 blockade indicates that castration-resistant prostate cancer frequently remains hormone driven. Cancer Res. **69,** 4937–4940
https://doi.org/10.1158/0008-5472.CAN-08-4531
Auchus R. J., Miller W. L. (1999): Molecular modeling of human P450c17 (17alpha-hydroxylase/17,20-lyase): insights into reaction mechanisms and effects of mutations. Mol. Endocrinol. **13,** 1169–1182
Auchus R. J. (2001): The genetics, pathophysiology, and management of human deficiencies of P450c17. Endocrinol. Metab. Clin. North. Am. **30,** 101–119
https://doi.org/10.1016/S0889-8529(08)70021-5
Auchus R. J. (2017): Steroid 17-hydroxylase and **17,**20-lyase deficiencies, genetic and pharmacologic. J. Steroid. Biochem. Mol. Biol. **165,** 71–78
https://doi.org/10.1016/j.jsbmb.2016.02.002
Berndt S. I., Wang Z., Yeager M., Alavanja M. C., Albanes D., Amundadottir L., Andriole G., Beane Freeman L., Campa D., Cancel-Tassin G. et al. (2015): Two susceptibility loci identified for prostate cancer aggressiveness. Nat. Commun. **5,** 6889
https://doi.org/10.1038/ncomms7889
Beuten J., Gelfond J. A., Franke J. L., Weldon K. S., Crandall A. C., Johnson-Pais T. L., Thompson I. M., Leach R. J. (2009): Single and multigenic analysis of the association between variants in 12 steroid hormone metabolism genes and risk of prostate cancer. Cancer Epidemiol. Biomarkers Prev. **18,** 1869–1880
https://doi.org/10.1158/1055-9965.EPI-09-0076
Biason-Lauber A., Leiberman E., Zachmann M. (1997): A single amino acid substitution in the putative redox partner-binding site of P450c17 as cause of isolated **17,**20-lyase deficiency. J. Clin. Endocrinol. Metab. **82,** 3807–3812
Brasso K., Thomsen F. B., Schrader A. J., Schmid S. C., Lorente D., Retz M., Merseburger A. S., von Klot C. A., Boegemann M., de Bono J. (2015): Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: A multicentre analysis. Eur. Urol. **68,** 317–324
https://doi.org/10.1016/j.eururo.2014.07.028
Brureau L., Moningo D., Emeville E., Ferdinand S., Punga A., Lufuma S., Blanchet P., Romana M., Multigner L. (2016): polymorphisms of estrogen metabolism-related genes and prostate cancer risk in two populations of African ancestry. PLoS One **13,** e0153609
https://doi.org/10.1371/journal.pone.0153609
Cabarkapa S., Perera M., McGrath S., Lawrentschuk N. (2016): Prostate cancer screening with prostate-specific antigen: A guide to the guidelines. Prostate Int. **4,** 125–129
https://doi.org/10.1016/j.prnil.2016.09.002
Cai C., Chen S., Ng P., Bubley G. J., Nelson P. S., Mostaghel E. A., Marck B., Matsumoto A. M., Simon N. I., Wang H., Chen S., Balk S. P. (2011): Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is upregulated by treatment with CYP17A1 inhibitors. Cancer Res. **71,** 6503–6513
https://doi.org/10.1158/0008-5472.CAN-11-0532
Cai L., Huang W., Chou K. C. (2012): Prostate cancer with variants in CYP17 and UGT2B17 genes: a meta-analysis. Protein Pept. Lett. **19,** 62–69
https://doi.org/10.2174/092986612798472848
Chang A. J., Autio K. A., Roach M., 3rd, Scher H. I. (2014): High-risk prostate cancer-classification and therapy. Nat. Rev. Clin. Oncol. **11,** 308–323
https://doi.org/10.1038/nrclinonc.2014.68
Chang B., Zheng S. L., Isaacs S.D., Wiley K. E., Carpten J. D., Hawkins G. A., Bleecker E. R., Walsh P. C., Trent J. M., Meyers D. A., Isaacs W. B., Xu J. (2001): Linkage and association of CYP17 gene in hereditary and sporadic prostate cancer. Int. J. Cancer **95,** 354–359
https://doi.org/10.1002/1097-0215(20011120)95:6<354::AID-IJC1062>3.0.CO;2-3
Chung B. C., Picado-Leonard J., Haniu M., Bienkowski M., Hall P. F., Shively J. E., Miller W. L. (1987): Cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. Proc. Natl. Acad. Sci. USA **84,** 407–411
https://doi.org/10.1073/pnas.84.2.407
Costa-Santos M., Kater C. E., Auchus R. J. (2004): Two prevalent CYP17 mutations and genotype-phenotype correlations in 24 Brazilian patients with 17-hydroxylase deficiency. J. Clin. Endocrinol. Metab. **89,** 49–60
https://doi.org/10.1210/jc.2003-031021
Damber J. E., Aus G. (2008): Prostate cancer. Lancet **371,** 1710–1721
https://doi.org/10.1016/S0140-6736(08)60729-1
de Bono J. S., Logothetis C. J., Molina A., Fizazi K., North S., Chu L., Chi K. N., Jones R. J., Goodman O. B. Jr., Saad F. et al. (2001):

Abiraterone and increased survival in metastatic prostate cancer. N. Engl. J. Med. **364,** 1995–2005 https://doi.org/10.1056/NEJMoa1014618

De Coster R., Wouters W., Bruynseels J. (1996): P450-dependent enzymes as targets for prostate cancer therapy. J. Steroid. Biochem. Mol. Biol. **56,** 133–143 https://doi.org/10.1016/0960-0760(95)00230-8

DeSantis C. E., Siegel R. L., Sauer A. G., Miller K. D., Fedewa S. A., Alcaraz K. I., Jemal A. (2016): Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer. J. Clin. **66,** 290–308 https://doi.org/10.3322/caac.21340

Dluzniewski P. J., Xu J., Ruczinski I., Isaacs W. B., Platz E. A. (2015): Polymorphisms influencing prostate-specific antigen concentration may bias genome-wide association studies on prostate cancer. Cancer Epidemiol. Biomarkers Prev. **24,** 88–93 https://doi.org/10.1158/1055-9965.EPI-14-0863

dos Santos A., Ribeiro M. L., Mesquita J. C., Carvalho-Salles A. B., Hackel C. (2002): No association of the 5‘ promoter region polymorphism of CYP17 gene with prostate cancer risk. Prostate Cancer Prostatic Dis. **5,** 28–31 https://doi.org/10.1038/sj.pcan.4500550

Douglas J. A., Zuhlke K. A., Beebe-Dimmer J., Levin A. M., Gruber S. B., Wood D. P., Cooney K. A. (2005): Identifying susceptibility genes for prostate cancer-a family-based association study of polymorphisms in CYP17, CYP19, CYP11A1, and LH-beta. Cancer Epidemiol. Biomarkers Prev. **14,** 2035–2039 https://doi.org/10.1158/1055-9965.EPI-05-0170

Eeles R. A., Olama A. A., Benlloch S., Saunders E. J., Leongamornlert D. A., Tymrakiewicz M., Ghoussaini M., Luccarini C., Dennis J. et al. (2013): Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat. Genet. **45,** 385–391 https://doi.org/10.1038/ng.2560

Ersekerci E., Sofikerim M., Taheri S., Demirtas A., Halis F. (2015): Genetic polymorphism in sex hormone metabolism and prostate cancer risk. Genet. Mol. Res. **14,** 7326–7334 https://doi.org/10.4238/2015.July.3.8

Estabrook R. W. (1999): Discovering the functions of cytochrome P450 in drug metabolism: the role of Alfred Hildebrandt. Drug Metab. Rev. **31,** 317–331 https://doi.org/10.1081/DMR-100101920

Fan Y. S., Sasi R., Lee C., Winter J. S., Waterman M. R., Lin C. C. (1992): Localization of the human CYP17 gene (cytochrome P450(17 alpha)) to 10q24.3 by fluorescence in situ hybridization and simultaneous chromosome banding. Genomics **14,** 1110–1111 https://doi.org/10.1016/S0888-7543(05)80140-5

Fizazi K., Flaig T. W., Stöckle M., Scher H. I., de Bono J. S., Rathkopf D. E., Ryan C. J., Kheoh T., Li J., Todd M. B., Griffin T. W., Molina A., Ohlmann C. H. (2016): Does Gleason score at initial diagnosis predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer? An analysis of abiraterone acetate phase III trials. Ann. Oncol. **27,** 699–705 https://doi.org/10.1093/annonc/mdv545

Fujimoto N. (2016): Role of the androgen-androgen receptor axis in the treatment resistance of advanced prostate cancer: from androgen-dependent to castration resistant and further. J. UOEH **38,** 129–138 https://doi.org/10.7888/juoeh.38.129

Gilep A. A., Sushko T. A., Usanov S. A. (2011): At the crossroads of steroid hormone biosynthesis: the role, substrate specificity and evolutionary development of CYP17. Biochim. Biophys. Acta **1814,** 200–209 https://doi.org/10.1016/j.bbapap.2010.06.021

Gsur A., Bernhofer G., Hinteregger S., Haidinger G., Schatzl G., Madersbacher S., Marberger M., Vutuc C., Micksche M. (2000): A polymorphism in the CYP17 gene is associated with prostate cancer risk. Int. J. Cancer **87,** 434–437 https://doi.org/10.1002/1097-0215(20000801)87:3<434::AID-IJC19>3.0.CO;2-G

Gudmundsson J., Sulem P., Gudbjartsson D. F., Blondal T., Gylfason A., Agnarsson B. A., Benediktsdottir K. R., Magnusdottir D. N., Orlygsdottir G., Jakobsdottir M. et al. (2009): Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat. Genet. **41,** 1122–1126 https://doi.org/10.1038/ng.448

Gudmundsson J., Sulem P., Rafnar T., Bergthorsson J. T., Manolescu A., Gudbjartsson D., Agnarsson B. A., Sigurdsson A., Benediksdottir K. R., Blondal T. et al. (2008): Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat. Genet. **40,** 281–283 https://doi.org/10.1038/ng.89

Habuchi T., Liqing Z., Suzuki T., Sasaki R., Tsuchiya N., Tachiki H., Shimoda N., Satoh S., Sato K., Kakehi Y. et al. (2000): Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. Cancer Res. **60,** 5710–5713

Haiman C. A., Stampfer M. J., Giovannucci E., Ma J., Decalo N. E., Kantoff P. W., Hunter D. J. (2001): The relationship between a polymorphism in CYP17 with plasma hormone levels and prostate cancer. Cancer Epidemiol. Biomarkers. Prev. **10,** 743–748

Hamada A., Danesi R., Price D. K., Sissung T., Chau C., Venzon D., Sparreboom A., Dahut W. L., Figg W. D. (2007): Association of a CYP17 polymorphism with overall survival in Caucasian patients with androgen-independent prostate cancer. Urology **70,** 217–220 https://doi.org/10.1016/j.urology.2007.06.1097

Han J. H., Lee Y. S., Kim H. J., Lee S. Y., Myung S. C. (2015): Association between cytochrome CYP17A1, CYP3A4, and CYP3A43 polymorphisms and prostate cancer risk and aggressiveness in a Korean study population. Asian J. Androl. **17,** 285–291 https://doi.org/10.4103/1008-682X.133320

Heinlein C. A., Chang C. (2004): Androgen receptor in prostate cancer. Endocr. Rev. **25,** 276–308 https://doi.org/10.1210/er.2002-0032

Henríquez-Hernández L. A., Valenciano A., Foro-Arnalot P., Álvarez-Cubero M. J., Cozar J. M., Suárez-Novo J. F., Castells-Esteve M., Fernández-Gonzalo P., De-Paula-Carranza B., Ferrer M. et al. (2015): Genetic variations in genes involved in testosterone metabolism are associated with prostate cancer progression: A Spanish multicenter study. Urol. Oncol. **33,** 331.e1–7 https://doi.org/10.1016/j.urolonc.2015.04.003

Hoffmann T. J., Passarelli M. N., Graff R. E., Emami N. C., Sakoda L. C., Jorgenson E., Habel L. A., Shan J., Ranatunga D. K, Quesenberry C. P. et al. (2017): Genome-wide association study of prostate-specific antigen levels identifies novel loci independent of prostate cancer. Nat. Commun. **8,** 14248 https://doi.org/10.1038/ncomms14248

Hoffmann T. J., Van Den Eeden S. K., Sakoda L. C., Jorgenson E., Habel L. A., Graff R. E., Passarelli M. N., Cario C. L., Emami N. C. et al. (2015): A large multiethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences. Cancer Discov. **5,** 878–891 https://doi.org/10.1158/2159-8290.CD-15-0315

Hornsby P. J., Yang L., Raju S. G., Maghsoudlou S. S., Lala D. S., Nallaseth F. S. (1992): Demethylation of specific sites in the 5-flanking region of the CYP17 genes when bovine adrenocortical cells are placed in culture. DNA Cell. Biol. **11,** 385–395 https://doi.org/10.1089/dna.1992.11.385

Huggins C., Stevens R. E. Jr., Hodges C. V. (1941): Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch. Surg. **43,** 209–223 https://doi.org/10.1001/archsurg.1941.01210140043004

Kakinuma H., Tsuchiya N., Habuchi T., Ohyama C., Matsuura S., Wang L., Nakamura A., Kato T. (2004): Serum sex steroid hormone levels and polymorphisms of CYP17 and SRD5A2:implication for prostate cancer risk. Prostate Cancer Prostatic Dis. **7,** 333–337 https://doi.org/10.1038/sj.pcan.4500753

Karimpur-Zahmatkesh A., Farzaneh F., Pouresmaeili F., Hosseini J., Azarghashb E., Yaghoobi M. (2013): A2 allele polymorphism of the CYP17 gene and prostate cancer risk in an iranian population. Asian Pac. J. Cancer Prev. **14,** 1049–1052 https://doi.org/10.7314/APJCP.2013.14.2.1049

Ketola I., Rahman N., Toppari J., Bielinska M., Porter-Tinge S. B., Tapanainen J. S., Huhtaniemi I. T., Wilson D. B., Heikinheimo M. (1999): Expression and regulation of transcription factors GATA-4 and GATA-6 in developing mouse testis. Endocrinology **140,** 1470–1480 https://doi.org/10.1210/endo.140.3.6587

Ketola I., Anttonen M., Vaskivuo T., Tapanainen J. S., Toppari J., Heikinheimo M. (2002): Developmental expression and spermatogenic stage specificity of transcription factors GATA-1 and GATA-4 and their cofactors FOG-1 and FOG-2 in the mouse testis. Eur. J. Endocrinol. **147,** 397–406 https://doi.org/10.1530/eje.0.1470397

Kiiveri S., Liu J., Heikkilä P., Arola J., Lehtonen E., Voutilainen R., Heikinheimo M. (2004): Transcription factors GATA-4 and GATA-6 in human adrenocortical tumors. Endocr. Res. **30,** 919–923 https://doi.org/10.1081/ERC-200044149

Kim Y. S., Kim Y., Choi J. W., Oh H. E., Lee J. H. (2016): Genetic variants and risk of prostate cancer using pathway analysis of a genome-wide association study. Neoplasma **63,** 629–634 https://doi.org/10.4149/neo_2016_418

Kittles R. A., Panguluri R. K., Chen W., Massac A., Ahaghotu C., Jackson A., Ukoli F., Adams-Campbell L., Isaacs W., Dunston G. M. (2001): Cyp17 promoter variant associated with prostate cancer aggressiveness in African Americans. Cancer Epidemiol. Biomarkers Prev. **10,** 943–947

Kwegyir-Afful A. K., Ramalingam S., Purushottamachar P., Ramamurthy V. P., Njar V. C. (2015): Galeterone and VNPT55 induce proteasomal degradation of AR/AR-V7, induce significant apoptosis via cytochrome c release and suppress growth of castration resistant prostate cancer xenografts in vivo. Oncotarget **6,** 27440–27460 https://doi.org/10.18632/oncotarget.4578

Latil A. G., Azzouzi R., Cancel G. S., Guillaume E. C., Cochan-Priollet B., Berthon P. L., Cussenot O. (2001): Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. Cancer **92,** 1130–1137 https://doi.org/10.1002/1097-0142(20010901)92:5<1130::AID-CNCR1430>3.0.CO;2-B

Lee-Robichaud P., Shyadehi A. Z., Wright J. N., Akhtar M. E., Akhtar M. (1995): Mechanistic kinship between hydroxylation and desaturation reactions: acyl-carbon bond cleavage promoted by pig and human CYP17 (P-450(17)alpha; 17 alpha-hydroxylase-17,20-lyase). Biochemistry **34,** 14104–14113 https://doi.org/10.1021/bi00043a015

Li Z., Bishop A. C., Alyamani M., Garcia J. A., Dreicer R., Bunch D., Liu J., Upadhyay S. K., Auchus R. J., Sharifi N. (2015): Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature **523,** 347–351 https://doi.org/10.1038/nature14406

Lin C. J., Martens J. W., Miller W. L. (2001): NF-1C, Sp1, and Sp3 are essential for transcription of the human gene for P450c17 (steroid 17alpha-hydroxylase/17,20 lyase) in human adrenal NCI-H295A cells. Mol. Endocrinol. **15,** 1277–1293

Lindström S., Wiklund F., Adami H. O., Bälter K. A., Adolfsson J., Grönberg H. (2006): Germ-line genetic variation in the key androgen-regulating genes androgen receptor, cytochrome P450, and steroid-5-alpha-reductase type 2 is important for prostate cancer development. Cancer Res. **66,** 11077–11083 https://doi.org/10.1158/0008-5472.CAN-06-3024

Liu H., Wang B., Han C. (2011): Meta-analysis of genome-wide and replication association studies on prostate cancer. Prostate **71,** 209–224 https://doi.org/10.1002/pros.21235

Locke J. A., Guns E. S., Lubik A. A., Adomat H. H., Hendy S. C., Wood C. A., Ettinger S. L., Gleave M. E., Nelson C. C. (2008): Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res. **68,** 6407–6415 https://doi.org/10.1158/0008-5472.CAN-07-5997

Lorente D., Mateo J., Zafeiriou Z., Smith A. D., Sandhu S., Ferraldeschi R., de Bono J. S. (2015): Switching and withdrawing hormonal agents for castration-resistant prostate cancer. Nat. Rev. Urol. **12,** 37–47 https://doi.org/10.1038/nrurol.2014.345

Loukola A., Chadha M., Penn S. G., Rank D., Conti D. V., Thompson D., Cicek M., Love B., Bivolarevic V., Yang Q. et al. (2004): Comprehensive evaluation of the association between prostate cancer and genotypes/haplotypes in CYP17A1, CYP3A4, and SRD5A2. Eur. J. Hum. Genet. **12,** 321–332 https://doi.org/10.1038/sj.ejhg.5201101

Lunn R. M., Bell D. A., Mohler J. L., Taylor J. A. (1999): Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). Carcinogenesis **20,** 1727–1731

https://doi.org/10.1093/carcin/20.9.1727
Madigan M. P., Gao Y. T., Deng J., Pfeiffer R. M., Chang B. L., Zheng S., Meyers D. A., Stanczyk F. Z., Xu J., Hsing A. W. (2003): CYP17 polymorphisms in relation to risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China. Int. J. Cancer **107,** 271–275
https://doi.org/10.1002/ijc.11378
Martinez-Arguelles D. B., Papadopoulos V. (2010): Epigenetic regulation of the expression of genes involved in steroid hormone biosynthesis and action. Steroids **75,** 467–476
https://doi.org/10.1016/j.steroids.2010.02.004
Miller W. L., Tee M. K. (2015): The post-translational regulation of **17,**20 lyase activity. Mol. Cell. Endocrinol. **408,** 99–106
https://doi.org/10.1016/j.mce.2014.09.010
Missaghian E., Kempna P., Dick B., Hirsch A., Ikhani-Koupaei R., Jegou B., et al. (2009): Role of DNA methylation in the tissue-specific expression of the CYP17A1 gene for steroidogenesis in rodents. J. Endocrinol. **202,** 99–109
https://doi.org/10.1677/JOE-08-0353
Mononen N., Seppälä E. H., Duggal P., Autio V., Ikonen T., Ellonen P., Saharinen J., Saarela J., Vihinen M., Tammela T. L. et al. (2006): Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors. Cancer Res. **66,** 743–747
https://doi.org/10.1158/0008-5472.CAN-05-1723
Montgomery B., Eisenberger M. A., Rettig M. B. Chu F., Pili R., Stephenson J. J., Vogelzang N. J., Koletsky A. J., Nordquist L. T., Edenfield W. J. et al. (2016): Androgen receptor modulation optimized for response (ARMOR) Phase I and II studies: Galeterone for the treatment of castration-resistant prostate cancer. Clin. Cancer Res. **22,** 1356–1363
https://doi.org/10.1158/1078-0432.CCR-15-1432
Nam R. K., Zhang W., Siminovitch K., Shlien A., Kattan M. W., Klotz L. H., Trachtenberg J., Lu Y., Zhang J., Yu C. et al. (2011): New variants at 10q26 and 15q21 are associated with aggressive prostate cancer in a genome-wide association study from a prostate biopsy screening cohort. Cancer Biol. Ther. **12,** 997–1004
https://doi.org/10.4161/cbt.12.11.18366
Nelson J. B., Lepor H. (2003): Prostate cancer: radical prostatectomy. Urol. Clin. North Am. **30,** 703–723
https://doi.org/10.1016/S0094-0143(03)00049-1
Ntais C., Polycarpou A., Ioannidis J. P. (2003): Association of the CYP17 gene polymorphism with the risk of prostate cancer: a meta-analysis. Cancer Epidemiol. Biomarkers Prev. **12,** 120–126
Okugi H., Nakazato H., Matsui H., Ohtake N., Nakata S., Suzuki K. (2006): Association of the polymorphisms of genes involved in androgen metabolism and signaling pathways with familial prostate cancer risk in a Japanese population. Cancer Detect. Prev. **30,** 262–268
https://doi.org/10.1016/j.cdp.2006.04.004
Panagiotou O. A., Travis R. C., Campa D., Berndt S. I., Lindstrom S., Kraft P., Schumacher F. R., Siddiq A., Papatheodorou S. I., Stanford J. L. et al. (2015): A genome-wide pleiotropy scan for prostate cancer risk. Eur. Urol. **67,** 649–657
https://doi.org/10.1016/j.eururo.2014.09.020
Pandey A. V., Miller W. L. (2005): Regulation of **17,**20 lyase activity by cytochrome b5 and by serine phosphorylation of P450c17. J. Biol. Chem. **280,** 13265–13271
https://doi.org/10.1074/jbc.M414673200
Picado-Leonard J., Miller W. L. (1987): Cloning and sequence of the human gene for P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): similarity with the gene for P450c21. DNA **6,** 439–448
https://doi.org/10.1089/dna.1987.6.439
Porubek D. (2013): CYP17A1: a biochemistry, chemistry, and clinical review. Curr. Top Med. Chem. **13,** 1364–1384
https://doi.org/10.2174/15680266113131200002
Risio M., Venesio T., Kolomoets E., Armaroli P., Gallo F., Balsamo A., Muto G., D'Urso L., Puppo P., Naselli A., Segnan N.; BECaP Working Group. (2011): Genetic polymorphisms of CYP17A1, vitamin D receptor and androgen receptor in Italian heredofamilial and sporadic prostate cancers. Cancer Epidemiol. **35,** 18–24
https://doi.org/10.1016/j.canep.2010.10.003
Rodriguez H., Hum D. W., Staels B., Miller W. L. (1997): Transcription of the human genes for cytochrome P450scc and P450c17 is regulated differently in human adrenal NCI-H295 cells than in mouse adrenal Y1 cells. J. Clin. Endocrinol. Metab. **82,** 365–371
https://doi.org/10.1210/jc.82.2.365
Rove K. O., Debruyne F. M., Djavan B., Gomella L. G., Koul H. K., Lucia M. S., Petrylak D. P., Shore N. D., Stone N. N., Crawford E. D. (2012): Role of testosterone in managing advanced prostate cancer. Urology **80,** 754–762
https://doi.org/10.1016/j.urology.2012.05.006
Ryan C. J., Smith M. R., de Bono J. S., Molina A., Logothetis C. J., de Souza P., Fizazi K., Mainwaring P., Piulats J. M., Ng S. et al. (2013): Abiraterone in metastatic prostate cancer without previous chemotherapy. N. Engl. J. Med. **368,** 138–148
https://doi.org/10.1056/NEJMoa1209096
Sarma A. V., Dunn R. L., Lange L. A., Ray A., Wang Y., Lange E. M., Cooney K. A. (2008): Genetic polymorphisms in CYP17, CYP3A4, CYP19A1, SRD5A2, IGF-1, and IGFBP-3 and prostate cancer risk in African-American men: the Flint Men's Health Study. Prostate **68,** 296–305
https://doi.org/10.1002/pros.20696
Schrade A., Kyrönlahti A., Akinrinade O., Pihlajoki M., Häkkinen M., Fischer S., Alastalo T. P., Velagapudi V., Toppari J., Wilson D. B., Heikinheimo M. (2015): GATA4 is a key regulator of steroidogenesis and glycolysis in mouse Leydig cells. Endocrinology **156,** 1860–1872
https://doi.org/10.1210/en.2014-1931
Schumacher F. R., Berndt S. I., Siddiq A., Jacobs K. B., Wang Z., Lindstrom S., Stevens V. L., Chen C., Mondul A. M., Travis R. C. et al. (2011): Genome-wide association study identifies new prostate cancer susceptibility loci. Hum. Mol. Genet. **20,** 3867–3875
https://doi.org/10.1093/hmg/ddr295
Setiawan V. W., Schumacher F. R., Haiman C. A., Stram D. O., Albanes D., Altshuler D., Berglund G., Buring J., Calle E. E., Clavel-Chapelon F. et al. (2007): CYP17 genetic variation and risk of breast and prostate cancer from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Cancer Epidemiol. Biomarkers Prev. **16,** 2237–2246

https://doi.org/10.1158/1055-9965.EPI-07-0589
Sewer M. B., Jagarlapudi S. (2009): Complex assembly on the human CYP17 promoter. Mol. Cell. Endocrinol. **300,** 109–114 https://doi.org/10.1016/j.mce.2008.10.006
Sewer M. B., Nguyen V. Q., Huang C. J., Tucker P. W., Kagawa N., Waterman M. R. (2002): Transcriptional activation of human CYP17 in H295R adrenocortical cells depends on complex formation among p54(nrb)/NonO, protein-associated splicing factor, and SF-1, a complex that also participates in repression of transcription. Endocrinology **143,** 1280–1290 https://doi.org/10.1210/endo.143.4.8748
Sewer M. B., Waterman M. R. (2002): Adrenocorticotropin/cyclic adenosine 3‘,5‘-monophosphate-mediated transcription of the human CYP17 gene in the adrenal cortex is dependent on phosphatase activity. Endocrinology **143,** 1769–1777 https://doi.org/10.1210/endo.143.5.8820
Sharma S., Zapatero-Rodríguez J., O‘Kennedy R. (2017): Prostate cancer diagnostics: Clinical challenges and the ongoing need for disruptive and effective diagnostic tools. Biotechnol. Adv. **35,** 135–149 https://doi.org/10.1016/j.biotechadv.2016.11.009
Sharp L., Cardy A. H., Cotton S. C., Little J. (2004): CYP17 gene polymorphisms: prevalence and associations with hormone levels and related factors. a HuGE review. Am. J. Epidemiol. **160,** 729–740 https://doi.org/10.1093/aje/kwh287
Shi X. B., Ma A. H., Xia L., Kung H-J., de Vere White R. W. (2002): Mutational analysis of 44 mutant androgen receptors from human prostate cancer. Cancer Res. **62,** 1496–1502
Siegel R. L., Miller K. D., Jemal A. (2017): Cancer Statistics, 2017. CA Cancer J. Clin. **67,** 7–30 https://doi.org/10.3322/caac.21387
Sissung T. M., Price D. K., Del Re M., Ley A. M., Giovannetti E., Figg W. D., Danesi R. (2014): Genetic variation: effect on prostate cancer. Biochim. Biophys. Acta **1846,** 446–456 https://doi.org/10.1016/j.bbcan.2014.08.007
Sivoňová M. K., Dobrota D., Dušenka R., Waczulíková I., Slezák P., Matáková T., Mahmoodová S., Mištuna D., Kliment J. (2012): Effect of CYP17 and PSA gene polymorphisms on prostate cancer risk and circulating PSA levels in the Slovak population. Mol. Biol. Rep. **39,** 7871–7880 https://doi.org/10.1007/s11033-012-1631-y
Small E. J., Halabi S., Dawson N. A., Stadler W. M., Rini B. I., Picus J., Gable P., Torti F. M., Kaplan E., Vogelzang N. J. (2004): Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J. Clin. Oncol. **22,** 1025–033 https://doi.org/10.1200/JCO.2004.06.037
Sobti R. C., Onsory K., Al-Badran A. I., Kaur P., Watanabe M., Krishan A., Mohan H. (2006): CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population. DNA Cell. Biol. **25,** 287–294 https://doi.org/10.1089/dna.2006.25.287
Sobti R. C., Gupta L., Singh S. K., Seth A., Kaur P., Thakur H. (2008): Role of hormonal genes and risk of prostate cancer: gene-gene interactions in a North Indian population. Cancer Genet. Cytogenet. **185,** 78–85 https://doi.org/10.1016/j.cancergencyto.2008.04.022
Song J., Tao Z. H., Liu X. Y., Gong S., Gan L. (2016): Relationship between CYP17 gene polymorphisms and risk of prostate cancer. Genet. Mol. Res. **15,** 15017866 https://doi.org/10.4238/gmr.15017866
Souiden Y., Mahdouani M., Chaieb K., Elkamel R., Mahdouani K. (2011): CYP17 gene polymorphism and prostate cancer susceptibility in a Tunisian population. Cancer Epidemiol. **35,** 480–484 https://doi.org/10.1016/j.canep.2010.11.008
Stanford J. L., Noonan E. A., Iwasaki L., Kolb S., Chadwick R. B., Feng Z., Ostrander E. A. (2002): A polymorphism in the CYP17 gene and risk of prostate cancer. Cancer Epidemiol. Biomarkers Prev. **11,** 243–247
Storbeck K. H., Swart A. C., Goosen P., Swart P. (2013): Cytochrome b5: novel roles in steroidogenesis. Mol. Cell. Endocrinol. **371,** 87–99 https://doi.org/10.1016/j.mce.2012.11.020
Suzman D. L., Antonarakis E. S. (2014): Castration-resistant prostate cancer: latest evidence and therapeutic implications. Ther. Adv. Med. Oncol. **6,** 167–1679 https://doi.org/10.1177/1758834014529176
Szulkin R., Karlsson R., Whitington T., Aly M., Gronberg H., Eeles R. A., Easton D. F., Kote-Jarai Z., Al Olama A. A., Benlloch S., Muir K. et al. (2015): Genome-wide association study of prostate cancer-specific survival. Cancer Epidemiol. Biomarkers Prev. **24,** 1796–1800 https://doi.org/10.1158/1055-9965.EPI-15-0543
Taioli E., Sears V., Watson A., Flores-Obando R. E., Jackson M. D., Ukoli F. A., de Syllos Cólus I. M., Fernandez P., McFarlane-Anderson N. et al. (2013): Polymorphisms in CYP17 and CYP3A4 and prostate cancer in men of African descent. Prostate **73,** 668–676 https://doi.org/10.1002/pros.22612
Taplin M. E., Bubley G. J., Ko Y. J., Small E. J., Upton M., Rajeshkumar B., Balk S. P. (1999): Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res. **59,** 2511–2515
Teerlink C. C., Leongamornlert D., Dadaev T., Thomas A., Farnham J., Stephenson R. A., Riska S., McDonnell S. K., Schaid D. J., Catalona W. J. et al. (2016): Genome-wide association of familial prostate cancer cases identifies evidence for a rare segregating haplotype at 8q24.21. Hum. Genet. **135,** 923–938 https://doi.org/10.1007/s00439-016-1690-6
Torre L. A., Sauer A. M., Chen M. S. Jr., Kagawa-Singer M., Jemal A., Siegel R. L. (2016): Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: Converging incidence in males and females. CA Cancer. J. Clin. **66,** 182–202 https://doi.org/10.3322/caac.21335
Vasaitis T. S., Bruno R. D., Njar V. C. (2011): CYP17 inhibitors for prostate cancer therapy. J. Steroid Biochem. Mol. Biol. **125,** 23–31 https://doi.org/10.1016/j.jsbmb.2010.11.005
Viger R. S., Mertineit C., Trasler J. M., Nemer M. (1998): Transcription factor GATA-4 is expressed in a sexually dimorphic pattern during mouse gonadal development and is a potent activator of the Müllerian inhibiting substance promoter. Development **125,** 2665–2675

Wadelius M., Andersson A. O., Johansson J. E., Wadelius C., Rane E. (1999): Prostate cancer associated with CYP17 genotype. Pharmacogenetics **9,** 635–639
https://doi.org/10.1097/00008571-199910000-00010

Wang F., Zou Y. F., Feng X. L., Su H., Huang F. (2011): CYP17 gene polymorphisms and prostate cancer risk: a meta-analysis based on 38 independent studies. Prostate **71,** 1167–1177
https://doi.org/10.1002/pros.21332

Wang Y., Zhang Y., Meng H., Hou X., Li Z., Liu Q., Meng L. (2015): Quantitative assessment of the association between CYP17 rs743572 polymorphism and prostate cancer risk. Cell. Biochem. Biophys. **71,** 983–991
https://doi.org/10.1007/s12013-014-0297-6

Wright J. L., Kwon E. M., Lin D. W., Kolb S., Koopmeiners J. S., Feng Z., Ostrander E. A., Stanford J. L. (2010): CYP17 polymorphisms and prostate cancer outcomes. Prostate **70,** 1094–1101
https://doi.org/10.1002/pros.21143

Xu B., Gao L., Cui Y., Gao L., Dai X., Li M., Zhang Y., Ma X., Diao F., Liu J. (2013): SET protein up-regulated testosterone production in the cultured preantral follicles. Reprod. Biol. Endocrinol. **11,** 9
https://doi.org/10.1186/1477-7827-11-9

Yamada T., Nakayama M., Shimizu T., Nonen S., Nakai Y., Nishimura K., Fujio Y., Okuyama A., Azuma J., Nonomura N. (2013): Genetic polymorphisms of CYP17A1 in steroidogenesis pathway are associated with risk of progression to castration-resistant prostate cancer in Japanese men receiving androgen deprivation therapy. Int. J. Clin. Oncol. **18,** 711–717
https://doi.org/10.1007/s10147-012-0430-8

Yamada Y., Watanabe M., Murata M., Yamanaka M., Kubota Y., Ito H., Katoh T., Kawamura J., Yatani R., Shiraishi T. (2001): Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (CYP17) and steroid 5alpha-reductase type II (SRD5A2) genes on prostate-cancer risk among the Japanese population. Int. J. Cancer **92,** 683–686
https://doi.org/10.1002/1097-0215(20010601)92:5<683::AID-IJC1255>3.0.CO;2-4

Yamaoka M., Hara T., Hitaka T., Kaku T., Takeuchi T., Takahashi J., Asahi S., Miki H., Tasaka A., Kusaka M. (2012): Orteronel (TAK-700), a novel non-steroidal **17,**20-lyase inhibitor: effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. J. Steroid. Biochem. Mol. Biol. **129,** 115–128
https://doi.org/10.1016/j.jsbmb.2012.01.001

Yanase T., Simpson E. R., Waterman M. R. (1991): 17 alpha-hydroxylase/17,20-lyase deficiency: from clinical investigation to molecular definition. Endocr. Rev. **12,** 91-108
https://doi.org/10.1210/edrv-12-1-91

Yap T. A., Carden C. P., Attard G., de Bono J. S. (2008): Targeting CYP17: established and novel approaches in prostate cancer. Curr. Opin. Pharmacol. **8,** 449–457
https://doi.org/10.1016/j.coph.2008.06.004

Yoshimoto F. K., Auchus R. J. (2015): The diverse chemistry of cytochrome P450 17A1 (P450c17, CYP17A1). J. Steroid. Biochem. Mol. Biol. **151,** 52–65
https://doi.org/10.1016/j.jsbmb.2014.11.026

Zhang L. H., Rodriguez H., Ohno S., Miller W. L. (1995): Serine phosphorylation of human P450c17 increases **17,**20-lyase activity: implications for adrenarche and the polycystic ovary syndrome. Proc. Natl. Acad. Sci. USA **92,** 10619–10623
https://doi.org/10.1073/pnas.92.23.10619

Zhu H., Garcia J. A. (2013): Targeting the adrenal gland in castration-resistant prostate cancer: a case for orteronel, a selective CYP-17 **17,**20-lyase inhibitor. Current. Oncol. Rep. **15,** 105–112
https://doi.org/10.1007/s11912-013-0300-1

Zhuang L., Johnson M. T. (2016): how precisely can prostate cancer be managed? Int. Neurourol. J. **20,** 120–130
https://doi.org/10.5213/inj.1632724.362

Zmuda J. M., Cauley J. A., Kuller L. H., Ferrell R. E. (2001): A common promotor variant in the cytochrome P450c17alpha (CYP17) gene is associated with bioavailability testosterone levels and bone size in men. J. Bone Miner. Res. **16,** 911–917
https://doi.org/10.1359/jbmr.2001.16.5.911

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