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The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer

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Abstract

The purpose of this review is to discuss the epidemiologic literature on the association of sex steroid hormones and components of their signaling and metabolic pathways with prostate cancer and to describe data evaluating racial variation in sex steroid hormone pathways as a possible explanation for the notably higher risk of prostate cancer in African-American men compared to white or Asian men. Although sex steroid hormones likely contribute to the growth and progression of prostate cancer, associations between hormones and prostate cancer risk across the range of normal levels have been difficult to reliably demonstrate epidemiologically. Methodologic issues no doubt have made the detection of these associations difficult. Of particular importance are (1) the inadequacy of measuring circulating hormones in middle age as a surrogate for the exposure in the target cells in the prostate at the relevant time in life and (2) the current inability to integrate across components of the sex steroid hormone signaling pathway to fully capture target cell androgenic and estrogenic stimulation. Although the approach of evaluating polymorphisms in genes involved in sex steroid hormone signaling or metabolism as a way to minimize some of the issues in the direct measurement of hormones is logical, the findings among these studies are somewhat difficult to reconcile as well. The problems of the changing case mix due to screening for elevated PSA, small sample sizes increasing the likelihood of false negative and false positive results, the controls and their allele frequencies not being representative of the population at risk, and lack of knowledge of the functional consequence of a polymorphism in relation to other polymorphisms in that gene or without consideration of other genes involved in the same pathway may be contributory. The primary result of the Prostate Cancer Prevention Trial confirms that intraprostatic dihydrotestosterone levels in the normal range indeed do contribute to the growth of prostate adenocarcinoma. However, the secondary result of higher-grade disease in cases in the finasteride arm coupled with clinical studies showing higher grade disease in non-metastatic cases with lower serum androgens, if not a pathological artifact or detection bias in the finasteride arm, possibly suggests a complex relationship between androgens and the growth versus differentiation of a prostate tumor. Finally, racial variation in components of the sex steroid hormone pathway do appear to exist, but whether the extent of the variation is adequately great such that it accounts for some of the substantial differences in prostate cancer incidence among blacks, whites, and Asians is unclear.

Keywords: Sex steroid hormones; Androgen receptor; Estrogen receptor; Male; Prostate cancer

1. Introduction

Sex steroid hormones contribute to the growth and progression of prostate cancer, but whether the range of normal levels is associated with prostate cancer risk has been difficult to reliably demonstrate. This review discusses the epidemiologic literature on the association of circulating concentrations of sex steroid hormones and polymorphisms in components of their signaling and metabolic pathways with prostate cancer and presents possible explanations for the inconsistencies among these studies. Also described

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are epidemiologic data suggesting that racial variation in sex steroid hormones and their signaling pathways may, in part, account for the 60% higher prostate cancer incidence in African-American men and the 38% lower incidence in Asian-American men compared to white men [1].

2. Sex steroid hormones

2.1. Androgens

Androgens are clearly important in the development, maturation, and the maintenance of the prostate, affecting both the proliferation and differentiation status of the luminal epithelium. Castration results in the involution of prostate gland as a result of diffuse atrophy primarily of the luminal epithelial cells, but not the stromal cells [2]. The replacement of androgen results in the proliferation of the epithelial cells, but once normal volume is attained additional androgenic stimulation does not further increase the size of the gland [3] as a result of a balance of proliferation and apoptosis [4]. Androgens also are determinants of the differentiated phenotype. Androgens contribute to the progression of prostate cancer in men. Indeed, blocking androgen production is commonly used to treat metastatic prostate cancer and is often successful in reducing the size of metastases and bone pain until androgen independent growth is acquired.

Although androgens are important in maintaining the prostate gland, whether an association exists between circulating concentrations of androgens and prostate cancer incidence has been difficult to demonstrate in epidemiologic studies. More than a dozen studies have measured testosterone, the major intraprostatic androgen dihydrotestosterone, the dihydrotestosterone metabolite androstanediol glucuronide, estrogens, or concentrations of other hormones (e.g., prolactin, leutinizing hormone, gonadotropin) in blood samples collected from middle-age and older men months to years prior to their diagnosis of prostate cancer and in a sample in men from the same cohort who were not diagnosed with prostate cancer [5–19]. Case-control studies in which hormone concentrations were measured in men who currently had prostate cancer and in a comparison group are not reviewed here because of methodologic issues that may limit their interpretability, such as the possible inhibition of hormone secretion by extant disease [20,21], use of cases who may have already been treated for prostate cancer, the use of men who clinically have benign prostatic hyperplasia, a condition that is also mediated by sex steroid hormones [22,23] as controls, and the use of younger controls, who on average would have higher testosterone concentrations than in the age group of men at risk for a diagnosis of prostate cancer.

Considering the 10 prospective studies that were published by 1998 in a meta-analysis performed by Eaton et al. [24], no difference in pre-diagnostic serum testosterone (ratio of mean testosterone in cases to controls = 0.99, 95% CI 0.95–1.02 in eight of the studies consisting of 817 cases and 2107 controls) or dihydrotestosterone (ratio of means = 0.98, 95% CI 0.94–1.03 in five of the studies consisting of 636 cases and 1040 controls) levels between men who were subsequently diagnosed with prostate cancer and controls was detected, except possibly for a slightly higher concentration of androstanediol glucuronide in the cases (ratio of means = 1.05, 95% CI 1.00–1.11 in five of the studies consisting of 644 cases and 1048 controls) [24]. Among these prospective studies, only a case-control study nested in the Physicians' Health Study ($n = 222$ pairs) observed the hypothesized direction of associations for the sex steroid hormones measured: testosterone and androstanediol glucuronide were statistically significant positively associated with prostate cancer, and estradiol and sex hormone binding globulin were inversely associated with prostate cancer [10]. In that prospective, study the mean time from blood draw to diagnosis was 6 years, and most of the cases were diagnosed because of an abnormal digital-rectal examination or symptoms during the era before the widespread use of screening for elevated serum PSA concentration. These findings were apparent only after simultaneous adjustment for all of the measured hormones and sex hormone binding globulin by multivariable analysis. In some of the prospective studies, the risk of prostate cancer was greater for a higher ratio testosterone to dihydrotestosterone [5,7,10,14].

Why has it been so difficult in well-designed epidemiologic studies to demonstrate that higher androgen concentrations are associated with a higher risk of prostate cancer? Perhaps most important is that it remains unsettled to what extent circulating concentrations of androgens correlate with intraprostatic levels. Of particular concern is the difficulty in capturing a relevant measure of dihydrotestosterone, which binds with greater affinity to the androgen receptor than does testosterone, and thus is more androgenic. Circulating dihydrotestosterone concentration itself may not be the optimal indicator of intraprostatic levels because of extra-prostatic contributions of this androgen from the testes as well as from skin and liver (catalyzed by 5α-reductase type 1). Circulating concentration of androstanediol glucuronide has been used as an indicator of the activity of 5α-reductase type 2, the enzyme that catalyzes the conversion of testosterone to dihydrotestosterone in the prostate [25], although whether serum androstanediol glucuronide concentration correlates with intraprostatic dihydrotestosterone level has not yet been proven.

Several other issues in the measurement of androgens should be considered as possible explanations for the inability to detect associations with prostate cancer. (1) Whether a single determination of serum androgens in middle or older age is representative of time-averaged or maximum levels over the etiologically relevant time of life is unknown. Across a short time span in middle age, intra-individual variability in androgen levels does not appear to be large. For example, in a study in which blood was draw from a group of 144 men on two occasions on average 3 years apart, the correlation between the two measures of the hormones concentrations were 0.68 for total testosterone, 0.66 for dihydrotestosterone,

0.74 for androstanediol glucuronide, 0.55 for estradiol, and 0.74 for sex hormone binding globulin (all $p < 0.0001$), after adjusting for age and race [18]. However, measurement in middle age ignores the potential for hormonal variation in utero at the time the prostate is formed, at puberty when the prostate matures to its adult size and functionality, and does not capture the slope of decline in androgens from early adulthood to older years. (2) If time of day of blood collection is not standardized for subjects then extraneous variability due to the pulsatile production of testosterone by the testis may obscure associations. However, despite these similar measurement issues and possible additional complexity of variation in duration of exposure to hormones by age at onset of menarche and menopause and the influence of reproduction on hormone levels, the association between estradiol and breast cancer has been fairly well established in prospective epidemiologic studies [26,27]. So although testosterone is likely important in the etiology of prostate cancer, the nature of the association is unlikely to simply be that chronic high testosterone exposure leads to greater proliferation of at risk prostate cells leads to a higher risk of prostate cancer.

Another methodologic issue of possible importance is the need to mutually statistically adjust the hormones and sex hormone binding globulin for one another to estimate the portion of these hormones that is free in circulation (<2% is unbound) and is available to cross the cell membrane to enter target cells. Dihydrotestosterone, testosterone, and estradiol as well as other 17β-hydroxysteroids all compete for noncovalent binding to sex hormone binding globulin, a major carrier protein in circulation. Lack of mutual statistical adjustment was put forth by Gann et al. as one possible explanation for the null results in the other prospective studies [10]. Indeed, in a reanalysis of population-based case-control data [28], Wolk et al. reported that after mutually statistically adjusting testosterone, estradiol, and sex hormone binding globulin, evidence for a positive association for testosterone and prostate cancer emerged, although it was not statistically significant [29]. However, no difference in the association for testosterone before and after mutual statistical adjustment for estradiol and sex hormone binding globulin was observed in a Finnish cohort study [14].

Additional analytical issues also need to be considered for why findings for androgens and prostate cancer risk among studies have been inconsistent and mostly not compatible with the androgen hypothesis. All of these studies have been hampered by the evaluation of a limited number of components of a large, complex and interrelated hormonal production, signaling, and metabolic pathway. The production of androgens is regulated by a negative feedback system to ensure normal range concentrations and bioavailability. Thus, whether an androgen level within the normal range in the majority of men is contributory to prostate cancer risk is questionable. An additional analytical issue that has emerged recently because of the routine use of screening for elevated serum PSA in the US is the changing mix of the nature of the case [30]. Before PSA screening was widely used in the US (pre-PSA era), cases were diagnosed because they were palpable or symptomatic, whereas in the PSA era cases are generally organ-confined and of small volume. These early lesions, many of which may never have been detected during a man's lifetime if the PSA test had not been done, do not necessarily have the same hormonal etiology as those cases that are detected clinically. Some of these screen-detected early lesions may be susceptible to the effects of androgens at a point later in their natural history, but because their natural history was interrupted by screening associations could not be detected.

Likely, because the prospective studies conducted to date have been modest in size, whether androgens may be more influential on the development of prostate cancer in certain subgroups of men has been rarely examined. How these men potentially at higher risk should be defined is not immediately obvious. Based on findings in some of our work in the Health Professionals Follow-up Study on obesity [31] and energy balance [32], both of which may influence hormonal systems, potentially susceptible groups may include men who are relatively young when diagnosed with prostate cancer or men who have a father or brother with prostate cancer. In addition to differential susceptibility among subgroups, the effects of androgens may be more evident in certain subgroups because of less obfuscation by competing mechanisms. For example, the association of androgens with prostate cancer might be more obvious in leaner men than in overweight and obese men [31] because in the latter men multiple physiologic systems are perturbed, including insulin and glucose control (poorer) and sex steroids (ratio of estrogens to androgens increases). The net effect of these perturbations in obese men, poor insulin and glucose control, which would be predicted to increase risk of prostate cancer, and increased ratio of estrogens to androgens, which would be predicted to decrease risk of prostate cancer, would tend to obscure associations between androgens and prostate cancer. Differences among the prospective studies on androgens and prostate cancer in the age distribution at diagnosis, the proportion with a positive family history, and the extent of overweight and obesity may explain some of the variability in findings among these studies.

Acknowledging the array of measurement and analytical issues, nevertheless prospective epidemiologic studies overall slightly hint that men who would be predicted to have higher intraprostatic levels of dihydrotestosterone based on higher levels of androstanediol glucuronide appear to have a higher risk of prostate cancer. This hint of a link is now supported by recent findings from the Prostate Cancer Prevention Trial. In that trial, 18,882 men aged 55+ years old (median = 63 years) who had serum PSA concentrations ≤3 ng/mL and a normal digital-rectal examination and never had been diagnosed with prostate cancer were randomized to take finasteride (5 mg/day), an inhibitor of 5α-reductase type 2, for 7 years or to placebo. The men underwent annual screening for prostate cancer by PSA test and digital rectal

examination, and if either was abnormal a biopsy was performed. At the end of the 7th year, the men who had not been diagnosed with prostate cancer during the course of the trial underwent biopsy irrespective of indication. At the time that the trial was stopped early by the Data Safety and Monitoring Board (because the result would not have changed with continuation to the planned end), the period prevalence of prostate cancer was 24% lower in the finasteride group than in the placebo group [33]. Because of the relatively short interval between the beginning and end of the trial (86% had completed the trial when it was stopped, so slightly less than 7 years on average), it is likely that many of the men ultimately diagnosed with prostate cancer likely already had one or more foci in place at the start of the trial. Thus, the primary result of the trial indirectly suggests that dihydrotestosterone is at least important in the promotion of the growth of existing small prostate tumors.

Interestingly, in the Prostate Cancer Prevention Trial, the period prevalence of higher-grade cases (Gleason sum 7–10) was greater in the finasteride arm than in the placebo arm. Of the 803 cancers detected in the 4368 men randomized to the finasteride arm, 280 were Gleason $\geq$7, whereas of the 1147 cases detected in the 4692 men randomized to the placebo arm, 237 were Gleason $\geq$7 [33]. Histologic grade (e.g., Gleason score) reflects the differentiation state of that tissue; that is, maintenance of the normal functional architecture of the tissue. However, much discussion has ensued about whether finasteride merely altered the visual appearance of the epithelium such that pathologists perceive worse histological patterns or whether finasteride enhanced the development of high-grade disease [34]. To explain the latter possibility, the action of dihydrotestosterone on transforming prostate epithelium must be considered: normal range intraprostatic levels of dihydrotestosterone may prevent the dedifferentiation of prostate epithelium within the nascent tumor by contributing to the maintenance of the epithelial phenotype via the activation of the androgen receptor and their joint transactivation of the transcription of genes that encode proteins normally produced by luminal epithelial cells. Thus, in the setting of low intraprostatic dihydrotestosterone due to finasteride treatment, the pressure to maintain differentiation may be lost. This hypothesis remains to be evaluated.

If not due to pathology artifact, or to diction bias, the findings for high grade-disease in the men with a finasteride-induced reduction in intraprostatic dihydrotestosterone levels in Prostate Cancer Prevention Trial may have been predicted from earlier clinical studies of non-metastatic prostate cancer in which men with lower serum testosterone [35,36] or free testosterone [37,38] had a higher mean Gleason score than did men with normal levels. Low was defined based on clinical norms. Lower circulating levels of testosterone possibly indirectly indicate lower prostatic levels of dihydrotestosterone, although how well circulating and intraprostatic androgen levels correlate is unresolved. In addition to having lower testosterone concentrations, men with high-grade disease also had lower mean estradiol levels compared to men with lower-grade disease [35]. Possibly compatible with these findings are results from the Health Professionals Follow-up Study, which despite showing no association between testosterone and total prostate cancer and for both higher and lower stage disease, showed a direct association of testosterone with low-grade prostate cancer, but an inverse association of testosterone with high-grade prostate cancer [18]. However, not all of the clinical studies are in agreement: a study in 370 prostate cancer cases without metastases showed no relation between serum testosterone (or estradiol) and Gleason grade (or stage) [39].

Attempts to isolate the possibly independent effects of androgens on histologic grade of prostate cancer from their effects on the tumor development are needed in future epidemiologic studies on the androgen hypothesis. For example, to partially replicate the context of the Prostate Cancer Prevention Trial, the association of serum androgens with high-grade versus low-grade disease should be evaluated among men with similarly low stage disease (e.g., T1c).

2.2. Estrogens

At the outset of most of the published studies, it was hypothesized that estrogens would protect against prostate cancer via inhibition of growth of prostate epithelial cells. As is the epidemiologic literature on androgens, the literature on the association of circulating estrogens is equally or possibly even more confusing. The Physicians' Health Study suggested that estradiol was inversely associated with prostate cancer risk after adjusting for sex hormone binding globulin and androgens [10]. The association for estradiol was not strictly decreasing [10]; risk was equally lower in each of the top quartiles, possible suggesting that low estradiol contributes to risk, rather than high estradiol is protective. The findings from other epidemiologic studies have indicated that estrogens may increase the risk of prostate cancer. In a prospective study in Rancho Bernado, CA, suggestive positive associations of plasma estradiol and estrone with prostate cancer were observed [6]. In a case-control study conducted in two New York counties, higher urinary excretion of 2-hydroxyestrone relative to 16α-hydroxyestrone was associated with a lower risk of prostate cancer [40]. The former metabolite has no estrogenic activity, whereas the latter is estrogenic [40].

Explanations for the variability in findings among the epidemiologic studies on estrogens, as for androgens, may be, in part, related to measurement issues. Plasma estradiol is present in pg/mL concentrations in men. Early assays for estradiol in men had poor sensitivity and poor reliability. Third generation radioimmunoassays have substantially improved measurement. The measurement issues described for androgens, including a single measurement in middle age and evaluation of only a small number of components of the sex steroid hormone-signaling pathway, also apply to estrogens. As described for studies of androgens, when evaluating the relation of estrogens to risk of prostate cancer

mutual statistical adjustment of androgens, estrogens, and sex hormone binding globulin is necessary. Because of the differential in binding affinities, a higher androgen level means greater displacement of estrogens yielding a higher bioavailable fraction of estrogens. Complicating the measurement of estrogens and the interpretation of the epidemiologic studies on serum steroid hormones is that estradiol may be produced intraprostatically via conversion of testosterone by aromatase expressed in stroma [41]. A small number of studies has examined polymorphisms in this enzyme, the results of which are described latter.

The nature of the effect of estrogens on prostate cancer risk may depend on the timing of exposure. In an animal model, high exposure to estrogens early in life promotes chronic inflammation in the prostate in adulthood [42]. Intraprostatic inflammation, which is a common finding in biopsy specimens [43], radical prostatectomy specimens [44] and in tissue resected for treatment of benign prostatic hyperplasia [45,46], is receiving renewed interest for its role in the etiology of prostate cancer [47]. At the present, it is not feasible in epidemiologic studies to directly evaluate how early life exposure to higher ranges of estrogens may influence risk of prostate cancer later in life, although some indirect evidence that obesity, as a possible indicator of a higher ratio of estrogens to androgens, early in life is associated with a lower risk of prostate cancer has been reported [48]. Pregnancy and birth characteristics has been inconsistently associated with risk of prostate cancer [49–51].

Aside from direct signaling by estrogen through its steroid receptor, estrogen may influence prostate cancer risk via its mutagenic metabolites. Certain catechol metabolites of estrogen, including 2-hydroxyestradiol and 4-hydroxyestradiol, may be converted in situ into DNA damaging agents [52]. This pathway may be of particular importance in men taking drugs like finasteride and dutasteride, in whom intraprostatic levels of testosterone may be increased by competition with these drugs for the catalytic site in the enzyme 5α-reductase type 2. The excess testosterone may be converted to estradiol in greater proportions than ordinarily. As a start to indirectly examine this hypothesis, polymorphisms in genes that encode enzymes that catalyze the generation of estrogen metabolites (*CYP1A1* and *CYP1B1*—described in this review below) or that detoxify these metabolites (*COMT* and *GST*s—not described in this review) have been evaluated in relation to prostate cancer.

3. Sex steroid hormone receptors and co-activators

3.1. The androgen receptor

The actions of testosterone and dihydrotestosterone in androgen-responsive tissues are mediated by the androgen receptor [53]. This receptor is sometimes mutated in prostate cancers with various predicted effects on its functionality [54] and possibly a wider array of activating steroid and non-steroid ligands [54,55]. The gene encoding this receptor, located on the long arm of the X chromosome, contains a variable length CAG repeat (encodes polyglutamine) in exon 1. In experimental constructs the fewer the number of CAG repeats, the greater the transactivational activity of the receptor [56,57]. The typical range of CAG repeats is 11–31 [58]. Human evidence for the significance of the length of this repeat is that men who inherit 40 or more androgen receptor gene CAG repeats suffer from Kennedy's disease (spinobulbar ataxia) [59,60]. This condition is characterized by androgen insensitivity due to the direct effect of the expansion of the CAG repeats on androgen receptor activity and progressive muscle weakness and atrophy as a result of the loss of brain motor neurons. It is unclear how expansion of the CAG influences this latter effect. Across the normal range of CAG repeat lengths there is evidence for differences in functional activity; men with longer CAG repeats were more likely to have defective sperm production than men with shorter repeats [61]. Shorter CAG repeat lengths are also associated with a higher risk of benign prostatic hyperplasia [62,63].

Several [64–70], but not all [18,71–80], epidemiologic studies support that shorter androgen receptor gene CAG repeats are associated with a higher risk of prostate cancer. Of these studies, three were prospective designs, one conducted largely in the pre-PSA era [67], one that straddled the PSA era [78] and one fully in the PSA-era [18]; differences in the case mix in these studies with similar design may explain some of their differences in findings. In the Physicians' Health Study, risk appeared to increase monotonically with decreasing CAG repeat number, but the association was limited to advanced cases [67]. On careful consideration, greater consistency was found among studies that included higher proportions of advanced cases or that were conducted in the pre-PSA era and in the stratum of men who had a young age at onset of prostate cancer [81]. Also, some variability in findings among the studies may be due to small sample sizes and the resultant imprecision in the estimation of the relative risk for extreme contrasts in number of CAG repeats.

A second polymorphic androgen receptor gene trinucleotide repeat has also been described in exon 1 consisting of GGN (*N*, any of the four nucleotides) repeats encoding polyglycine [82]. This repeat is not as polymorphic as the CAG repeat; about 85–90% of individuals have the most prevalent allele or one longer [83]. The association between the androgen receptor gene GGN repeat has not been consistent among studies [64,66,68,71,76,78,84,85]. Contributing to the inconsistency in findings is the use of different criteria for counting the number of repeats (e.g, GGC only versus GGN) and the use of different repeat length classification schemes for modeling (e.g., short versus long, most common versus less common).

One other polymorphism in the androgen receptor gene has been evaluated. Two studies have reported positive associations between the S1 allele (variant allele, leads to loss of restriction site) for the StuI restriction site polymorphism at codon 211 (G1733A) in exon 1 and prostate cancer risk in

younger African-American men [86] and high grade disease in Portuguese prostate cancer cases [87]. This polymorphism is in linkage disequilibrium with the CAG and GGN repeats [87] and thus whether this polymorphism has effects independent of the repeated sequences is unknown.

Further attempts to clarify the relation of repeated sequences in the androgen receptor gene with prostate cancer risk may include considering the joint association of the CAG and GGN repeats and the joint associations of circulating androgen concentrations with both of the repeats. Although several studies have evaluated interactions between the two repeated sequences [64,66,68,71,76,78,84], substantially larger sample sizes are needed to evaluate the joint associations at cutpoints other than the mean/median for both repeats, which tend to be conservative and may result in the inability to statistically detect interactions. As for circulating hormones, the association of these androgen receptor gene repeats may be most apparent in advanced cases, in particular those detected in the era prior to the widespread screening for elevated PSA or in susceptible subgroups (e.g., defined by age or family history) or in subgroups where obfuscation by competing pathways is limited (e.g., normal weight men). Given the findings of the PCPT, future analyses should pay particular attention to the relation of the CAG and GGN repeats with high- and low-grade disease. Perhaps more difficult to evaluate in epidemiologic studies is the role of alternative ligands that activate the androgen receptor, such as estradiol when coupled with certain steroid receptor co-activators [88].

3.2. The estrogen receptor

The prostate expresses both α and β estrogen receptors (ER) at low levels [89]. Expression of ERα appears to be limited to the stroma [90]. ERα, but not ERβ, is essential for prostate development [42]. Unlike the androgen receptor, only a handful of case-control studies have evaluated polymorphisms in the ERα gene, located on the long arm of chromosome 6. Several polymorphisms have been evaluated in relation to prostate cancer in up to three studies each (Table 1). Other sequence variants have been identified in ERα in prostate cancer cases or in controls, but their prevalences are too low [91] to feasibly investigate in relation to prostate cancer. These studies are small by current standards, having roughly 100–200 case-control pairs and all are retrospective. Although limited in number and size, these studies indicate that more work on the role of ERα in the etiology of prostate cancer is needed. No studies have been conducted for polymorphisms in ERβ and risk of prostate cancer.

3.3. Co-activator amplified in breast cancer (AIB)-1

Sex steroid hormone receptors require co-activators/co-regulators for signaling, including the androgen receptor ARA co-regulators [92] and the estrogen receptor AIB-1 co-activator [93]. The AIB-1 gene (also known as SRC-3), located on chromosome 20, contains a long and polymorphic CAG/CAA repeat sequence, encoding a polyglutamine (Q) tract [93]. Only 1% of individuals have repeat lengths other than 29, 28, or 26 [94,95]. Though the biological effect of this polymorphism on coactivator function has not been examined, it may possibly influence prostate cancer risk by modulating estrogen, androgen, or other steroid receptor function. The *AIB-1*26/26 genotype was related to lower risk of extraprostatic disease compared to other genotypes in nested case-control study [95]. In a Chinese case-control study, compared to the 29/29 genotype, other *AIB-1* genotypes were associated with a higher risk of prostate cancer [96]. The implication of the findings from these two

Table 1
Polymorphism in the estrogen receptor-α and risk of prostate cancer

Polymorphism	Association with prostate cancer
GGGA repeat in intron 1	Variant length repeat genotypes vs. $(GGGA)_5$/(GGGA) (wild type): OR = 4.6, 95% CI 0.99–21.67, but not with age at onset, stage, or grade [91]
T → C, intron 1, PvuII restriction site (CATCTG)	C/C (restriction site absent) vs. T/T: OR = 1.85, 95% CI 0.90–3.81 [77] T/T (restriction site present) vs. C/C: OR = 3.44, 95% CI 1.97–5.99 [146] No association [147]
A → G, intron 1, XbaI restriction site	G/G (restriction site absent) vs. A/A: OR = 1.65, 95% CI 0.70–3.92 [77] G/G (restriction site absent) vs. A/A: OR = 0.58, 95% CI 0.33–1.01 [146]
TCC → TCT, codon 10, synonymous–serine–S	TCC/TCC vs. TCT/TCT: OR = 3.26, 95% CI 1.58–6.73), but not with stage [147] No association [91]
GCC → GCC, codon 87, synonymous–alanine-A	No association [91] GCC not present in cases or controls [147]
CGC → CGT, codon 243, synonymous–arginine–R	No association [91,147]
CCC → CCG, codon 325, synonymous–proline-P	CCG/CCG or CCC/CCG vs. CCC/CCC OR of higher grade = 3.0, 95% CI 1.4–6.4 OR of advanced stage = 2.4, 95% CI 1.1–5.1 OR of bone metastases = 3.1, 95% CI 1.4–6.8 [87] No association [91,147]
ACG → ACA, codon 594, synonymous–threonine–T	No association [91,147]

studies is not directly apparent. In the former study, the 26/26 genotype was uncommon and is probably not important for prostate cancer at least in the white population [95]. Nevertheless, because of their importance in steroid hormone signaling, the identification of polymorphisms in principal co-activators and co-regulators of androgen receptor and estrogen receptor activation is needed.

4. Sex steroid hormone synthesis and metabolism

Shown in figure is the androgen and estrogen synthetic and metabolic pathway in the testis, prostate, and liver (excluded adrenal sources for simplicity) and the genes that catalyze the steps in the pathway. Many of the genes in this pathway are polymorphic, although with the exception of *SRD5A2*, encoding 5α-reductase type 2, and *CYP17*, encoding steroid 17α-hydroxylase/17,20 lyase, variations in these genes have been understudied for their relation with prostate cancer. The recent availability of high-throughput technology has contributed to recent flurry of publications evaluating polymorphisms in many of the other genes involved in androgen and estrogen synthesis and metabolism; however, the majority of these studies are small to moderate sized retrospective case-control studies in which it is unclear whether the comparison group would be expected to have the same underlying allele frequencies as the population that gave rise to the cases, which is required for validity. Inconsistency in the findings among these studies may perhaps be due to differences in the target populations, differences in the source and extent of bias, and chance variability because of small size relative to the prevalence of alleles. Gene candidates have been selected with good rationale for the most part, although the function of particular polymorphisms has not always been characterized. Most of these studies have not considered the joint associations of these polymorphic genes with each other or with circulating hormone concentrations. Substantially larger studies will be needed to do so. As for the studies on circulating hormones and their receptors, additional clarity may be gained in future studies by considering the nature of the cases (e.g., stage, grade, PSA era) and subgroups (e.g., family history, young age, normal weight). Many of the genes involved in hormone metabolism are highly polymorphic, and as a few groups have started to do (e.g. [97–99]), evaluation of haplotypes and diplotypes may better classify individuals with respect to the production, stability, or activity of the enzyme in question.

The current state of knowledge of the associations of polymorphisms in *SRD5A2* and *CYP17* with prostate cancer is described below. Findings for polymorphisms in genes encoding other enzymes involved in the synthesis or metabolism of androgens or estrogens are summarized in Tables 2 and 3, respectively. Because of the present scarcity of research, at this time no conclusions may be drawn about the importance of the polymorphisms in *HSD3B1*, *HSD3B2*, *HSD17B3*, *CYP3A4*, *CYP19*, *CYP1A1*, and *CYP1B1* in the etiology of prostate cancer. The functional significance of many of these polymorphisms is unknown. Clearly, more work is needed to understand the influence of normal sequence variants in these genes on risk of prostate cancer and it pathological characteristics.

4.1. Steroid 17α-hydroxylase/17,20 lyase (CYP17)

The enzyme encoded by *CYP17* catalyzes two reactions in testosterone synthesis pathway (figure), pregnenolone to 17α-hydroxypregnenolone via its 17α-hydroxylase activity and the latter to dehydroepiandrosterone via its 17,20 lyase activity in the testis [100]. *CYP17* is located on the long arm of chromosome 10. In a meta-analysis of 10 case-control studies published through 2002, there was no overall association between a substitution of C for T in *CYP17* that exists 34 basepairs upstream of the translation start site, but downstream of the transcription start site and prostate cancer [101]. Subsequent case-control studies also did not observe an association [97,102]. One recently published case-control study in China suggested a higher risk of prostate cancer for having at least one T allele [103]. The effect of this polymorphism on the production, stability, or activity of the enzyme is unknown, but does not appear to influence circulating hormone concentrations in men [103–105].

4.2. Steroid 5α-reductase type 2 (SRD5A2)

The conversion of testosterone to dihydrotestosterone is catalyzed in the prostate by 5α-reductase type 2 (Fig. 1), which is encoded by SRD5A2 on chromosome 2. Dihydrotestosterone has greater affinity for the androgen receptor, resulting in greater transactivation of androgen-responsive genes. Genetically male individuals who are deficient in this enzyme because of mutation [106] exhibit pseudohermaphroditism prior to puberty, but become more phenotypically male during puberty [107] due to conversion of testosterone to dihydrotestosterone catalyzed by 5α-reductase type 1 expressed in skin.

Several polymorphic regions in *SRD5A2* have been identified. A TA dinucleotide repeat in the 3′-untranslated region, a leucine (L) substitution for valine (V) at codon 89, which reduces enzyme activity in vitro, and a threonine (T) substitution for alanine (A) at codon 49 substitution, which results in a higher enzymatic activity, have been evaluated in relation to prostate cancer risk. No variation in serum concentration of androstanediol glucuronide has been observed by length of the TA repeat [108]. However, men with at least one threonine allele for the A49T polymorphism had lower androstanediol glucuronide [108] and men with both leucine alleles for V89L possibly may have lower plasma androstanediol glucuronide levels [109,110].

Five studies have observed evidence against the hypothesized effect of the TA repeat (i.e., that longer repeats would be associated with a higher risk) [75,109,111–113]. A Canadian case-control study noted a 2.5-fold higher risk of prostate

Table 2
Association of polymorphisms in genes that are involved in androgen synthesis or metabolism with prostate cancer

Gene	Enzyme activity	Polymorphism	Association with prostate cancer
HSD17B3			
Expressed in testis	17β-hydroxysteroid dehydrogenase type 3 metabolizes androstenedione to testosterone	Glycine (G-GGT → Serine (S-AGT), codon 289	Serine/serine or glycine/serine vs. glycine/glycine: OR = 2.5, 95% CI 1.03–6.07 [148].
CYP3A4	Nifedipine oxidase deactivates testosterone via hydroxylation	A → G, nucleotide-290	G/G or A/G vs. A/A: OR = 2.7, 95% CI 0.77–7.66 (prospective study of men with BPH followed for 11 years) [149] G/G or A/G vs. A/A African-Americans: OR = 4.1, 95% CI 1.3–12.2 Whites: OR = 2.3, 95% CI 1.1–4.5 Nigerians: no positive association Findings possibly attributable to population stratification [150] G/G or A/G vs. A/A: worse clinical characteristics at diagnosis Whites: OR of high stage = 2.10, 95% CI 1.09–4.05 [151] African-Americans: OR of high grade = 1.6, 95% CI 0.7–3.6 [152].
		A → G, nucleotide −392	G/G or A/G vs. A/A No association with prostate cancer overall Whites OR of nonaggressive = 0.08, 95% CI 0.01–0.59 OR of high aggressive = 1.91, 95% CI 1.02–3.57 African-Americans No association with disease aggressiveness [97,153]
HSD3B1			
Expressed in prostate	3β-hydroxysteroid dehydrogenase type I metabolize dihydrotestosterone to inactive metabolites	Asparagine (N) → threonine (T), codon 367	Threonine/threonine or asparagines/threonine vs. asparagine/asparagine: OR = 1.50, 95% CI 1.04–2.17 [154]
		T → C, nucleotide 7062	No association [154]
HSD3B2			
Expressed in testes	3β-hydroxysteroid dehydrogenase type 2 metabolizes dihydrotestosterone to inactive metabolites	C → T, nucleotide 7474, 3′ untranslated region	No association [154]
		C → G, nucleotide 7519. 3′ untranslated region	No association [154]
			Threonine/threonine or asparagines/threonine at codon 367 and G/G or C/G at nucleotide 7519 vs. asparagine/asparagine and C/C: sporadic: OR = 1.61, 95% CI 1.07–2.42; familial: OR = 2.17, 95% CI 1.29–3.65 [154]

cancer for the valine allele at codon 89 in men undergoing biopsy for elevated PSA/DRE [114]. Also, men with prostate cancer who were prospectively followed were at a higher risk of biochemical progression (i.e., PSA re-elevation months to years after prostatectomy) if they carried the valine allele [114]. A case-control study in Japan reported a higher risk of prostate cancer for the valine allele, but no association with grade or stage [115]. Other studies suggest that leucine homozygotes were more likely to have metastatic disease [116], are more likely to experience biochemical failure [117], or have a higher risk of prostate cancer [75,97]. No statistically significant inverse association has been found for the V89L polymorphism and prostate cancer in several other studies [100,109,112,116,118–121], including prospective studies [110,113]. Also, the V89L polymorphism was not clearly associated with tumor pathological characteristics [118]. The A49T substitution was associated with a higher risk of prostate cancer or poorer grade disease in some studies [112,118,122], but not elsewhere [75,97,113,116,121,123]. A meta-analysis of the studies reporting on the A49T, V89L,

Table 3
Association of polymorphisms in genes that are involved in estrogen synthesis or metabolism with prostate cancer

Gene	Enzyme activity	Polymorphism	Association with prostate cancer
CYP19	Aromatase catalyses the conversion of testosterone to estradiol in fat and in prostate stroma [41]	Arginine (C nucleotide) → cysteine (T nucleotide), codon 264	Arginine/cysteine (C/T) vs. arginine/arginine (C/C): OR = 2.50, 95% CI 0.99–6.28 (T/T not observed) [77]
			Cysteine/cysteine (T/T) vs. arginine/arginine (C/C): OR of total = 2.08, 95% CI 1.20–3.64 OR of high grade = 5.50, 95% CI 3.16–9.59 [146]
		$(TTTA)_n$ in intron 4	171 vs. 167 base-pair allele: OR = 1.58, 95% CI 1.00–2.51 187 vs. 167 base-pair allele: OR = 1.41, 95% CI 1.01–1.98 [75].
CYP1A1	Aryl hydrocarbon hydroxylase catalyzes the conversion of estradiol to 2-hydroxyestradiol [52] and the activation of environmental carcinogens such as polyaromatic hydrocarbons	Isoleucine (I–A nucleotide at 2455) → valine (V-G nucleotide at 2455), codon 462	
			Valine/valine vs. isoleucine/isoleucine OR = 2.4, 95% CI 1.01–5.57 [155] OR of total prostate cancer = 1.91, 95% CI 1.09–3.32 OR of high vs low grade = 1.60, 95% CI 0.93–2.63 OR of high vs low stage = 4.04, 95% CI 2.35–6.96 [156] G allele (valine) less common in cases than in controls ($p = 0.03$) [99].
		T → C, nucleotide 3801, gain Msp I restriction site	C/C or T/C vs. T/T: OR of total prostate cancer = 1.40, 95% CI 1.03–1.90 OR of high vs. low grade = 2.04, 95% CI 1.23–3.38 OR of high vs. low stage = 4.51, 95% CI 2.46–8.27 [156] C/C vs. T/T: OR = 2.35, 95% CI 0.89–6.26 [157] C allele less common in cases than in controls ($p = 0.001$) [99]
		Haplotype for T3801C, A2455G, and C2453A	T-A-C haplotype more common in cases than in controls C-A-C haplotype less common in cases than in controls [99].
CYP1B1	Aryl hydrocarbon hydroxylase catalyzes the conversion of estrogens to 4-hydroxyestradiol [52] and the metabolism of environmental carcinogens	Alanine (A-G at nucleotide 355) → serine (S–T at nucleotide 355), codon 119	Serine/serine (T/T) vs. alanine/alanine: OR = 4.02, 95% CI 1.73–9.38 [158]
			Serine/serine (T/T) and alanine/serine (G/T) more common in sporadic cases than in controls ($p = 0.8$), but not more common in familial cases ($p = 0.55$) [98].
		A → G, nucleotide-1549	No association [98].
		C → T, nucleotide-1001	T/T and C/T less common in sporadic cases than controls ($p = 0.04$), but not less common in familial cases [98]
		G → A, nucleotide-263	A/A and G/A less common in sporadic cases than in controls ($p = 0.03$), but not less common in familial cases [98]
		C → T, nucleotide-13	No association [158] T/T and C/T less common in sporadic cases than in controls ($p = 0.02$), but not less common in familial cases [98]
		Arginine (R-C at nucleotide 142) → glycine (G-G at nucleotide 142), codon 48	No association [158] G/G and C/G less common in sporadic cases than in controls ($p = 0.04$), but not less common in familial cases [98]
		Leucine (L-C at nucleotide 4326) → valine (V-G at nucleotide 4326), codon 432	No association [98,158]
		C (nucleotide 4379) → T (nucleotide 4379), codon 449(aspartate-D-synonymous)	No association [98,158]

Table 3 (*Continued*)

Gene	Enzyme activity	Polymorphism	Association with prostate cancer
		asparagine (N-A at nucleotide 4390) → serine (S-G at nucleotide 4390), codon 453	Serine allele not observed [158]
			G/G and A/G more common in sporadic ($p = 0.11$) and familial cases ($p = 0.14$) than in controls [98]
		C → A, nucleotide 3653 T → G, nucleotide 5359 A → G, nucleotide 5639 A → T, nucleotide 7072	No association [98]
		Haplotype for C–1001T, G–263A, C–13T, C142G, T355G	C–G–C–C–G haplotype more common in sporadic cases than in controls (p = 0.29), but not more common in familial cases T–A–T–G–T haplotype less common in sporadic cases than in controls ($p = 0.057$), but not more common in familial cases [98].

and the TA repeat polymorphisms in relation to prostate cancer through 2002 reported summary odds ratios for the threonine versus alanine allele of 1.56, and when omitting the Makridakis et al. [122] results, the study that initially reported a positive association, of 1.08 (95% CI 0.72–1.61), for the leucine versus valine allele of 1.02 (95% CI 0.94–1.11), and for longer versus shorter TA repeats 0.85 (95% CI 0.64–1.12) [124]. Another polymorphism, C682G, which is located 12 nucleotides upstream of the transcription start in the 5′-untranslated region, was not associated with sporadic prostate cancer in a case-control study [121].

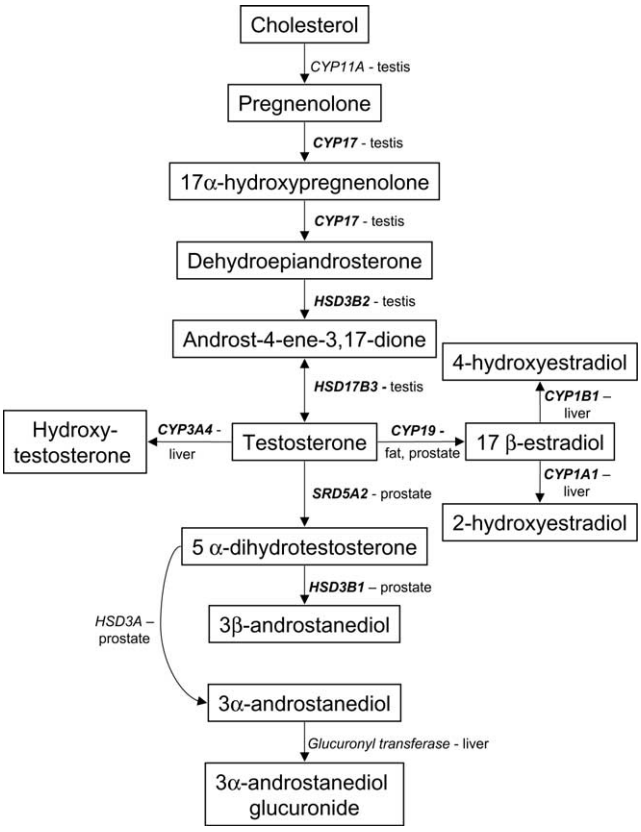

Fig. 1. Steroid hormone synthesis and metabolism in the testis, prostate, and liver. Polymorphic enzymes reviewed in Tables 2 and 3 are indicated in bold.

At the present, there is no compelling evidence for a strong effect of polymorphisms in *SRD5A2* on risk of prostate cancer. However, more work is needed to define the influence of polymorphisms in *SRD5A2* in relation to early versus advanced prostate cancer, grade of disease, and survival with prostate cancer.

5. Racial variation in sex steroid hormones and hormone signaling

Racial variation in prostate cancer incidence and mortality rates in the US is pronounced. African-American men have the highest prostate cancer incidence rate (standardized to 2000 US population age standard, 1992–1999: 275.3 per 100,000 men annually) and mortality rate (75.1 per 100,000 men annually) among any racial or ethnic group in the US. By comparison, the incidence and mortality rates are 1.6 (172.9 per 100,000 men) and 2.3 (32.9 per 100,000 men) times that for whites, respectively. Prostate cancer incidence and mortality rates for Asian/Pacific Islander, American Indian/Alaskan Native, or Hispanic are substantially lower than those for white Americans [125]. In addition to prostate cancer being more frequently diagnosed in African-American men, the putative precursor lesion for prostate cancer, high-grade prostatic intraepithelial neoplasia is seen at an earlier age and is more prevalent and extensive in African-American compared to white men based on a large autopsy series [126].

The notable variation in the incidence of prostate cancer among American black, white, and Asian men may be due to heterogeneity in inherent and modifiable determinants of prostate epithelial cell growth and differentiation, although the specific factors have been elusive. Even after adjusting for purported dietary and lifestyle risk factors for prostate cancer, risk of prostate cancer is elevated in black versus white US health professionals [127]. Another hypothesis to explain the variability in prostate cancer incidence across racial groups is normal range differences among men of different races in components of the androgen signaling pathway beginning during gestation through old age [128].

Evidence for racial variation in circulating concentrations of sex steroid hormones and in the prevalence of polymorphisms in steroid receptors and enzymes involved in the synthesis or metabolism of hormones is discussed and future research needs are described.

5.1. Sex steroid hormones

In some modest sized cross-sectional studies [25,129–132], adult African-American men have had higher mean circulating concentrations of testosterone or other androgens than similarly aged white men, with differences in levels being greater in young adulthood (10–20% [25,129]) than in mid-adulthood (3% [130]). Statistically significant differences in testosterone concentration between middle-aged and older black and white men were not seen in two studies [127,133,134]. In a subset of 483 black and 695 white men aged 24–30 years old at baseline who participated in the CARDIA study, black men had a 3% higher mean serum testosterone concentration than white men after adjusting for age, body mass index at baseline and change in body mass index over three assessments of hormones in blood samples that spanned 8 years [135]. The slopes of the decrease in testosterone with age were similar between black and white men. After further adjusting for baseline waist circumference and change in waist circumference (the African-American men had smaller waist circumference at baseline and a steeper increase in waist circumference over time than did the white men) the racial difference in testosterone concentration was essentially eliminated. No racial differences were observed in sex hormone binding globulin or free testosterone. The CARDIA study highlights the possibility that the observed racial variability in hormone levels is not necessarily due to inherent differences between racial groups, but instead may be due to racial differences in factors that contribute to hormone levels (e.g., body mass index and waist circumference are inversely correlated with testosterone [136]). On the other hand, observed differences in body habitus among racial groups may be due to inherent differences in systemic hormone levels.

Variability by race in in utero exposure to maternal androgens has also been evaluated. Mean blood testosterone concentration was roughly 50% higher among African American women in the first trimester of pregnancy than age- and week-of-gestation matched white women in one study [137]. A second study also found a statistically significantly higher maternal testosterone concentration at the time of labor in black women even after adjustment for known predictors of maternal testosterone levels; however no difference by race in cord blood testosterone concentration was detected (black 19.9, white 20.6 ng/dL) [138]. Racial differences were not observed for estrogens in maternal blood or in cord blood. Umbilical cord blood hormone concentrations reflect the combination of fetal, placental, and maternal contributions, which is assumed to reflect the fetal hormonal milieu. However, testosterone concentration in males is at the nadir at birth compared to midway through gestation. Whether racial variability in fetal testosterone production exists during gestation is not known. Although testosterone concentrations are at their lowest point at birth, additional evaluation of this hypothesis is needed using cord blood samples after exclusions for pregnancy conditions that are known to influence hormone levels (e.g., pre-eclampsia) and adjusting for non-inherent determinants of hormone levels that may also differ by race (e.g., parity).

5.2. Sex steroid hormone receptors

Many studies have now observed that African-American men have on average fewer androgen receptor gene CAG repeats than whites, typically a two repeat difference [58,64,127,139–144]. Some [58,64,139], but not all [127], studies have found that Asian men have a greater number of repeats (mean of ∼0.5–1.0 difference) than whites. One study also considered Hispanic white men, who had a mean that was one repeat longer than whites [143]. Although the mean difference in repeat length is small, we have previously estimated that the two repeat decrement on average between blacks and whites might account for as much as a 15% higher risk of prostate cancer [127]. How much of the difference in risk of prostate cancer between black and white men would be accounted for by the combination of shorter CAG repeats on average, and integrating over age, the possibly higher circulating testosterone concentration, and thus, intraprostatic androgen levels on average in black compared to white men, has not been estimated.

5.3. Sex steroid hormone synthesis and metabolism

The prevalences of polymorphisms in a number of genes that catalyze the synthesis or the inactivation of androgens and estrogens vary by race. Some of the apparent differences in allele frequencies by race may be merely due to chance variation because of small sample sizes, especially when estimating the frequencies of less common alleles. We do not review the literature on this area, but instead point to two examples given by Zeigler-Johnson et al. [145] who reported consistent racial variation in the prevalence of polymorphisms in *SRD5A1* and *CYP3A4* across studies. Pooling over studies, Zeigler-Johnson et al. reported the prevalence of the variant allele for the valine 89 leucine polymorphism in *SRD5A2* to be 0.55 in Asians, 0.30 in whites, 0.31 in Hispanics, 0.23 in African-Americans, and 0.19 in Africans [145]. Racial variation in the alanine to glycine substitution upstream of the *CYP3A4* start site is even more pronounced with variant allele frequencies of 0 in Asians, 0.07 in whites, 0.58 in African-Americans, and 0.77 in Africans [145]. Although allele frequencies may vary drastically from race to race, the association between a given polymorphism and prostate cancer may not necessarily differ by race (unless the prevalence of modifying factors of the relation between the polymorphism and prostate

cancer also differs by race). What may differ, however, is the proportion of the risk of prostate cancer in a particular racial group that is attributable to a given polymorphism. Despite any racial variation in the frequencies of alleles for genes encoding hormone metabolism enzymes, it remains to be demonstrated whether any of these polymorphisms are associated with risk of prostate cancer, irrespective of race.

6. Conclusions

Epidemiologic evidence that normal variation in circulating concentrations of androgens, estrogens, and sex hormone binding globulin, normal sequence variation in genes that encode the androgen and estrogen receptors, and normal sequence variation in genes that encode enzymes involved in the biosynthesis or the inactivation of androgens and estrogens contribute to the development of prostate cancer is weak to modest at the present. The primary result of the Prostate Cancer Prevention Trial confirms that physiologic intraprostatic dihydrotestosterone levels are permissive for the growth of prostate adenocarcinoma. However, the secondary result of higher-grade disease in men in the finasteride arm coupled with clinical studies showing higher-grade disease in non-metastatic cases with lower serum androgens, if not a pathologic artifact or detection bias in the finasteride arm, possibly suggests a complex relationship between androgens and the growth versus differentiation status of a prostate tumor. Finally, racial variation in individual components of the sex steroid hormone pathway does exist. However, when considered individually, none of these components appears to account for the large differences in prostate cancer incidence among blacks, whites, and Asians.

Several critical challenges have been presented in studying the hormone hypothesis, possibly the most important among them is the adequacy of measuring the hormone exposure relevant to the target cells in the prostate at the relevant time in life. Related to this challenge is the current inability to integrate across components of the sex steroid hormone signaling pathway to fully capture target cell androgenic and estrogenic stimulation, including alternative ligands for these receptors. Statistical methods such as path analysis may be useful to address this concern, once some of the measurement issues are resolved.

The findings from studies of genetic variation in genes encoding the androgen and estrogen receptors and enzymes involved in hormone synthesis and metabolism in relation to prostate cancer are somewhat difficult to reconcile. The problems of changing case mix, small sample sizes increasing the likelihood of false negative and false positive results, and allele frequencies in the controls being dissimilar to those in the population that gave rise to the cases are well recognized. The sample size concern may be addressed through pooling of data as is currently being done in the National Cancer Institute-sponsored Cohort Consortium (http://ospahome.nci.nih.gov/cohort/). Difficulties in interpretation may also arise in genetic association studies of prostate cancer because typically only a single polymorphism is considered, often without knowledge of its functional consequence or its relation to other polymorphisms in that gene, or without consideration of other genes involved in the same pathway. Evaluation of haplotypes and diplotypes to complement alleles and genotypes is now in fashion, although the effectiveness of this approach remains to be demonstrated.

A major challenge in prostate cancer epidemiology is to uncover whether variability in the sex steroid hormone pathway contributes to the higher risk of prostate cancer in African-American men and the lower risk of prostate cancer in Asian men, both compared to white men. The possibly minor physiologic effects of sequence variants that differ among the racial groups in genes involved in hormonal pathway may sum to have sufficient differences in biological activity on the prostate such that racial differences in the incidence of prostate cancer would be detectable. Possible biological effects of genetic polymorphisms that vary by race and that might influence risk of prostate cancer later in life that should be evaluated include the early life factors age at onset of puberty and the rate of prostate growth and maturation.

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