# Racial Differences in the Androgen/Androgen Receptor Pathway in Prostate Cancer

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Pathologic and epidemiologic data suggest that while little racial variation exists in prostate cancer prevalence ("autopsy cancer"), striking racial variation exists for the clinically diagnosed form of the disease. A review of the available literature was performed to define whether racial differences in serum androgen levels or qualitative or quantitative differences in the androgen receptor were correlated with prostate cancer incidence or severity. Black men were found to be exposed to higher circulating testosterone levels from birth to about age 35 years. Such differences were not consistently noted among older men. Significant differences also were found for dihydrotestosterone metabolites among black, white, and Asian men. Unique racial genetic polymorphisms were noted for the gene for 5α-reductase type 2 among black and Asian men. Novel androgen receptor mutations recently have been described among Japanese, but not white, men with latent prostate cancer. Finally, androgen receptor gene polymorphisms leading to shorter or longer glutamine and glycine residues in the receptor protein are correlated with racial variation in the incidence and severity of prostate cancer. This same polymorphism also could explain racial variation in serum prostate-specific antigen levels. Collectively, these data strongly suggest racial differences within the androgen/androgen receptor pathway not only exist but could be one cause of clinically observed differences in the biology of prostate cancer among racial groups. (*J Natl Med Assoc.* 1999;91:653-660.)

**Key words:** prostate cancer ◆ race ◆ serum hormone levels ◆ androgen receptor

Striking differences among races exist in the incidence of and mortality from prostate cancer. The incidence is 50% higher and mortality two times higher in American black men than in American white men.[1] In contrast, Asian Americans have both a lower incidence of and lower mortality from prostate cancer.[1,2] Mebane et al[3] reported that the age at onset of clinically manifest prostate cancer is about 5 years younger in American blacks (age 45, 6.7 cases per 100,000) than in American whites (age 50, 2.6 cases per 100,000) and that when stratified by age, black men have a two-fold higher incidence of metastasis at diagnosis. What factors are responsible for such overt differences in the clinically manifest form of the disease?

Pathologic data are informative in this regard. In a large autopsy series, Sakr et al[4] showed that the prevalences of small, clinically undetected ("latent") prostate cancers in men who died of other causes were similar for black and white men when stratified by age. However, when both autopsy and clinical specimens were analyzed for the presence of the pre-

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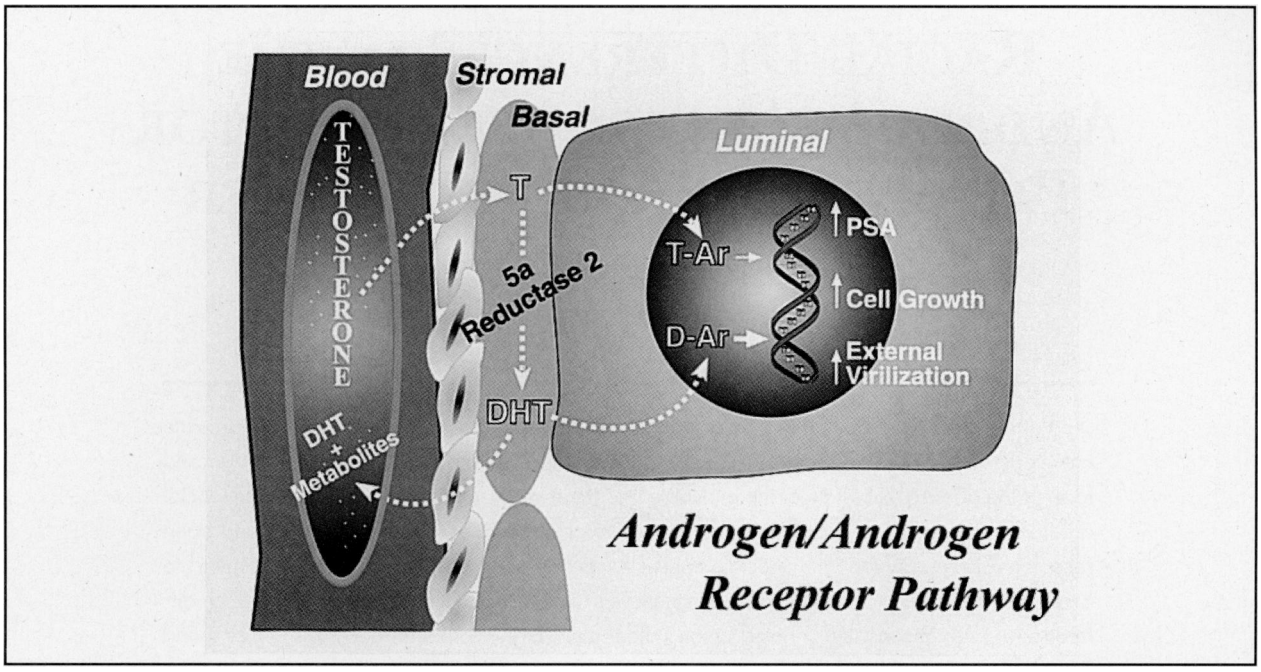


**Figure 1.** Androgen/androgen receptor pathway within the prostate and urogenital tract. Testosterone from the blood diffuses into hormonally responsive tissues where it either binds directly to the androgen receptor (AR) or is converted to its more potent dihydrotestosterone (DHT) form by the enzyme 5α-reductase type II. Once the receptor is bound with either ligand, it becomes activated and can bind to the promoter of androgen-responsive genes, triggering protein synthesis. Processes regulated by this pathway include prostate-specific antigen production (PSA), cell growth, and the development of male secondary sexual characteristics.

malignant lesion high-grade prostatic intraepithelial neoplasia (HGPIN), black men between the ages of 30 and 59 years had both a higher incidence and a greater extent of HGPIN compared with age-matched white men.[4] The molecular mechanism for this recent observation awaits elucidation. However, as differences in HGPIN between the races also are associated with earlier onset of prostate cancer in black men, the question arises of whether the same mechanisms also explains why black Americans progress at a higher rate to a clinically manifest form of prostate cancer.

This article examines the major factors within the androgen/androgen receptor pathway that may be involved in the early progression of prostate cancer in black Americans as well as perceived racial differences in the behavior of the disease among different racial groups.

## ANDROGEN/ANDROGEN RECEPTOR PATHWAY

Figure 1 presents a simplified diagram of the androgen/androgen receptor pathway within the prostate and urogenital tract.[5-7] The receptor pathway involves the steroid hormones testosterone and dihydrotestosterone (DHT), the androgen receptor (AR), and target genes in the nucleus that are regulated by androgens. Testosterone diffuses into the prostate from the blood, where it can bind directly to the AR. Of more physiologic importance, testosterone is converted to DHT via the enzyme 5α-reductase type II.

Observations indicate that this enzymatic activity is compartmentalized to stromal and basal cells of the prostate and is not found in luminal cells (which are enriched for AR expression).[8] This localization suggests a paracrine interaction between the ligand (DHT) produced in the basal-stromal cell compartment and the receptor (AR) produced in the luminal cell compartment. After binding of ligand to receptor, the receptor is activated, it binds to responsive elements within the promoter regions of androgen-responsive genes, and transcription and subsequently protein synthesis occur.[5] Such androgen-regulated

genes include those responsible for proliferation, prostate-specific antigen (PSA) expression, or virilization of the urogenital sinus.[9]

## Androgens

Testicular androgens[6,7] have a major influence on the development of the normal prostate and play at least a permissive role in the development of neoplasia. Testosterone is the major circulating androgen in the blood. Males achieving castrate levels of testosterone prior to puberty (eunuchs) do not develop benign prostatic hypertrophy or prostate cancer. In contrast, rats supplemented with testosterone have a more than 18-fold increase in prostate cancer incidence.[10]

The adrenal androgens androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate can also be converted to testosterone and DHT; however, they provide <10% of the circulating androgens and do not support the growth and development of the normal prostate. They may, however, play a significant role in advanced prostate cancer as a residual source of testosterone and DHT or by directly binding to mutant ARs.[11] Dihydrotestosterone is the potent intracellular mediator of the androgenic effect in the prostate and external genitalia. It is formed by reduction of testosterone by the enzyme 5α-reductase type II (one of two isoforms, produced mainly in the urogenital tract). The enhanced efficacy of DHT compared with testosterone is partially mediated by its higher affinity for and stability of binding to the AR. However, higher concentrations of testosterone may compensate in part for its weaker interaction with the receptor.[12] Receptor activation and subsequent transcription are complex and may involve growth factors, vitamins, or neurotransmitters.[6,13]

Congenital syndromes of androgen resistance such as absence of 5α-reductase type II or defects in androgen receptor function result in various forms of the male pseudohermaphrodite syndrome, in which prostatic development and male external virilization are inhibited despite the presence of testosterone in utero. Of interest, at puberty, when there is a gonadotropin-induced rise in testosterone, males with 5α-reductase type II deficiency become virilized and DHT becomes detectable in the serum. This is related to production of DHT by 5α-reductase type I (the other isoform) produced in the skin and liver. [5-7,14]

After its formation in the tissues, very little DHT reenters the plasma; it is metabolized to androstanediol glucuronide and androsterone glucuronide, which are detectable in serum. Thus, the levels of these metabolites are more reflective of tissue DHT levels and 5α-reductase activity than are serum DHT levels.[6]

## Serum Androgen Levels and Prostate Cancer

Experimental and clinical observations would suggest that the measurement of serum androgens might explain differences in prostate cancer among and between populations, as testosterone and DHT appear to be integral factors for its development. Early studies by Ghanadian et al[15] and Ahluwalia et al[16] revealed small increases in serum testosterone levels but no differences in DHT levels in prostate cancer cases compared with matched control subjects. However, in the latter study, only US black men had higher testosterone levels than their controls; Nigerian men with prostate cancer had lower testosterone levels than age-matched control subjects.[16]

In a subsequent study, Osegbe and Ogunlewe[17] also found decreased levels of serum testosterone in prostate cancer cases compared with control subjects. De Jong et al[18] compared serum androgen levels among Dutch and native Japanese men (who have low prostate cancer incidence) with and without prostate cancer. Although Dutch men exhibited marginally higher testosterone levels than Japanese men, there was no difference in testosterone or DHT levels between Dutch or Japanese cases and age-matched control subjects.

Thus, the data from retrospective case-control studies are at best controversial with respect to the correlation of serum androgen levels with the development of prostate cancer. The interpretation of the above-mentioned studies is potentially difficult because of a variety of covariables that can affect serum androgen levels, such as age, body habitus, cigarette smoking, ethanol intake, and medications. In addition, due to the high prevalence of asymptomatic prostate cancer in the population, especially prior to the era of detection by PSA testing, the ascertainment of "control" subjects is problematic. It is also uncertain what effect prostate cancer itself may have on serum androgen levels.

More recent strategies have been to collect data and serum from men who either did or did not develop prostate cancer with prolonged follow-up (12-14 years).[19-21] After prospective ascertainment of prostate cancer and control subjects, the serum samples stored many years prior are analyzed for differences in androgen levels between cases and controls. The results of three such studies have been

reported. Nomura et al[19] found that prostate cancer cases exhibited serum testosterone levels similar to, but DHT levels lower than, those of control subjects. The testosterone/DHT ratio was slightly higher in serum from patients with prostate cancer. Barrettt-Connor et al[20] also found no differences in testosterone levels but noted a significant increase in androstenedione (androgen precursor) in prostate cancer patients; DHT levels were not measured. Hsing and Comstock[21] found marginal but statistically insignificant increases in serum testosterone and the testosterone/DHT ratio in serum from prostate cancer patients.

Thus, three prospective studies provide only meager data to suggest a role for serum androgens in the development of prostate cancer. However, important caveats exist. Men in these studies were at least 50 years of age when samples were taken. As testosterone levels decrease with age, it is unknown whether at an earlier age androgen levels would be different among men destined to develop prostate cancer. In addition, tissue DHT is the important mediator of the intracellular androgenic effect. Unfortunately, none of the above-mentioned studies measured levels of the serum metabolites of DHT.

## RACIAL DIFFERENCES IN ANDROGEN LEVELS AND 5α-REDUCTASE ACTIVITY

Because of the higher incidence of clinically diagnosed prostate cancer and the earlier age of onset (beginning in the mid-40s) among American blacks, recent studies have attempted to define differences in the hormonal milieu of this racial group compared with other racial groups with a lower prostate cancer risk. Henderson et al[22] measured serum hormonal levels among black and white women during gestation and found that black women exhibited 48% higher testosterone levels when matched for age, weight, day of gestation, and birthweight of offspring.

Ross et al[23] found that young black men (18-22 years) had serum testosterone levels 15% higher than those of age-matched white men. Their results were confirmed by Ellis and Nyborg,[24] who found that young black men had higher serum testosterone levels than whites of similar age and weight and with similar times of sample procurement. Of interest, this difference in testosterone levels was noted only in black men up to age 35. Subsequently, there was no difference in testosterone levels.[24]

In a follow-up study, Ross et al[25] measured serum testosterone, DHT, and metabolites of DHT among young American blacks and whites and native Japanese. In this study, both black and white men had significantly higher serum levels of DHT metabolites (androsterone glucuronide, 3α,17β-androstanediol glucuronide) than did native Japanese men. In addition, black men had 11% higher testosterone levels than whites (not significant), but serum testosterone levels were similar between black and Japanese men. These data suggest the possibility that lower 5α-reductase activity in Japanese men is correlated with their decreased incidence of prostate cancer.[25] Lookinbill et al[26] documented decreased 5α-reductase activity in young native Chinese men and women compared with their age-matched white counterparts.

Reichardt et al[27] described genetic polymorphisms in the gene encoding the 5α-reductase type II enzyme, which is located on chromosome 2 (2p23). In comparing allele frequencies for three US population groups (blacks, Asian Americans, and non-Hispanic whites), they noted three different allele families (containing 87 base pairs [bp], 103-107 bp, and 121-131 bp). Of interest, 18% of black American men exhibited the 121-131 bp alleles. No such alleles were noted in white or Chinese men. These same investigators reported the presence of a prevalent germline polymorphism in the 5α-reductase type II gene, which substitutes a valine for a leucine at codon 89.[28] The leucine allele frequency was highest in Asian Americans and associated with significantly decreased 5α-reductase type II activity in Asian-American patients who had homozygous leucine, as opposed to valine, alleles. Thus, when considered together, the data collected from populations of young black, Asian, and white men provide evidence of significant biochemical and genetic differences that correlate with racial disparities in prostate cancer incidence.

## RACIAL DIFFERENCES IN ANDROGEN RECEPTOR MUTATIONS

The AR is a member of the steroid receptor superfamily and functionally acts as a ligand-activated nuclear transcription factor. The AR gene is located on the X chromosome (q11- 12) and consists of an amino-terminal transactivation domain, a central DNA-binding domain, and a carboxy-terminal ligand-binding domain.[29] As the effects of testosterone and DHT are mediated through the interaction of these hormones with the AR, the question arises of whether qualitative or quantitative differ-

ences in the AR could explain differences in the incidence of or mortality from prostate cancer among and between races. Several studies have shown that AR gene mutations are rare in clinically localized prostate cancer but tend to occur with increasing frequency in patients with metastatic disease.[9,30,31] Such mutations involve the ligand-binding domain and confer altered specificity of binding that results in enhanced functional activity and relative androgen-independent behavior.[30,31]

Racial differences with respect to such mutations in advanced disease have not been reported. From a functional standpoint, two recent studies have shown that black and white patients with advanced disease treated with androgen ablation had similar survival rates.[32,33] In addition, Fowler et al[34] showed that the PSA nadirs after androgen ablation were similar for blacks and whites, as were the responses to the addition or withdrawal of the antiandrogen flutamide. These data suggest that if AR differences exist among black and white patients with advanced prostate cancer, they are of minimal functional significance given existing therapy.

In a comparative study, novel AR mutations were described in native Japanese and American men using samples of both clinically diagnosed and clinically inapparent cancer discovered at the time of autopsy (latent cancer).[35] No AR mutations were found in any of the clinically discovered Japanese (0/38) or American (0/26) prostate cancer cases. However, 17 (23%) of 74 Japanese men compared with 0 of 43 American men with latent cancer at autopsy were found to have AR mutations. These mutations were frameshift, nonsense, and missense types, which would be predicted to result in loss of function of the AR. Whether such mutations are responsible for the low progression rate of prostate cancer to clinically diagnosed disease in Japanese men is uncertain but provocative.

Quantitative differences in AR expression have been shown by Sadi et al[36] to correlate poorly with response to androgen ablation. Subsequently, the same authors showed that heterogeneity of AR staining within a specimen predicted a shorter duration of response.[37] To date, quantitative studies on racial variation in AR expression in men with and without prostate cancer have not been reported.

## RACIAL VARIATION IN AR GENE POLYMORPHISMS

The amino-terminal domain of the AR consists of lengths of glutamine and glycine repeats, which are encoded by CAG and GGC trinucleotide repeats, respectively, within the AR gene.[29] The numbers of glutamine (CAG) and glycine (GGC) repeats within the normal population are polymorphic and vary from 7 to 35 for CAG and 4 to 24 for GGC.[38,39]

Mutations that lead to an overexpansion of the AR CAG repeat length are associated with at least three genetic diseases. One of these, X-linked spinal and bulbar atrophy (Kennedy's disease), is a degenerative neuromuscular syndrome in which the CAG repeat is twice the normal length.[39,40] In this syndrome, longer CAG repeat length correlates with disease severity and earlier age at onset of the disease.[40] Androgen receptors from patients with Kennedy's disease exhibit reduced transcriptional activity. Chamberlain et al[40] also have confirmed that altering the number of CAG repeats affects transcriptional activation without affecting ligand binding; deletion of CAG repeats resulted in increased transcriptional activity, whereas addition decreased functional activity.

Three studies described the potentially important association of trinucleotide repeat length with the incidence or severity of prostate cancer.[39,41,42] Irvine et al[41] studied both CAG and GGC repeat length in black, white, and Asian American populations. They found that the median CAG repeat length of Asian Americans was 22, whereas 75% of black Americans and 62% of white Americans exhibited a CAG repeat length $<22$. With respect to the GGC repeat, 70% of Asian men exhibited 16 repeats, while only 20% of black and 57% of white men did. In a comparison of white prostate cancer patients with control subjects, a genotype of "$<22$ CAG repeats and not 16 GGC repeats" was associated with a relative risk of prostate cancer of 2.1 ($P=.08$). This high-risk genotype was present in 25 (64%) of 39 black men, 9 (24%) of 37 white men, and 3 (9%) of 34 Asian men, which correlates with their respective prostate cancer risk.

Giovannucci et al[42] studied CAG repeats in 587 prostate cancer patients and 588 control subjects from the Physician's Health Study. A significant trend of prostate cancer diagnosis overall was noted for men with $\leq 18$ CAG repeats in comparison with men with $\geq 26$ repeats. However, when stratified by grade and stage of cancer, shorter CAG repeat length was significantly related to high-grade and high-stage prostate cancer ($P=.001$) versus low-grade or low-stage cases. This association of advanced

stage of disease with shorter CAG repeat length subsequently was confirmed by Hakimi et al.[39] In addition, these authors noted a higher frequency of short GGC alleles (≤14 repeats) in patients with prostate cancer than in the general population.

## RACIAL VARIATION IN SERUM PSA LEVELS ANDROGEN/ANDROGEN RECEPTOR-MEDIATED TRANSCRIPTIONAL EVENTS

Considering the above-described racial differences in hormonal profiles and the AR, one could speculate that differences in expression of proteins that are mediated via the androgen/androgen receptor pathway could be found. Prostate-specific antigen is a relatively tissue-specific glycoprotein produced by prostate epithelial cells. Serum PSA measurements are invaluable for the detection, staging, and monitoring of response to therapy in prostate cancer.[43]

Variations in serum PSA levels are associated with the volume of benign and cancerous epithelium, cancer grade and stage, access to the circulation of PSA (affected by trauma and inflammation), and cellular production of PSA (affected by the androgen/androgen receptor pathway and other nonandrogen PSA stimulatory factors).[14,44-46] In addition, a number of recent studies have shown a striking racial variation in serum PSA values.[47-52] Serum PSA values appear to be higher in black Americans with or without a cancer diagnosis than in white Americans.[47-49,51,52] In contrast, serum PSA levels appear lower in Japanese men than in age-matched white men.[50]

To evaluate whether racial factors independently contribute to variability in serum PSA levels, we recently analyzed radical prostatectomy specimens from 40 black and 148 white men who underwent prostatectomy at our center during the same time period. Cancer grade, stage, tumor volume (using the whole-mount technique), and prostate weight, as well as the number and location of cancer foci, were analyzed in depth in black and white patients.[53] The data revealed that serum PSA levels in black and white patients were similar among patients with cancers of lower pathologic stage (organ-confined cancers [pathologic stage T2], organ-confined cancers with iatrogenic-positive margins [T2+], or cancers with extraprostatic extension but negative margins [T3-]). However, among cases in which the seminal vesicles were involved (T3c) or in which extraprostatic extension and positive surgical margins (T3+) were found, serum PSA levels were significantly higher in the black patient cohort despite tumor volumes, prostate weights, and grades of prostate cancer similar to those of the white cohort. This result suggests a difference in cellular production or metabolism of PSA between races. This was confirmed in a multivariate analysis that revealed both race and tumor volume were independent contributors to serum PSA variation in patients with advanced cancers. Because all but two patients exhibited undetectable PSA levels immediately after surgery, the source of serum PSA was attributable to the prostatectomy specimen rather than occult distant metastases.[53]

Prostate-specific antigen production is an androgen-regulated process, and racial differences in either the ligand or receptor conceivably could result in variation in PSA production. However, a recent study was unable to correlate serum-free testosterone, androstenedione, luteinizing hormone, or prolactin levels with serum PSA levels in a multivariate analysis of black and white patients with stages A-C prostate cancer.[54]

An alternative explanation for racial variation in serum PSA levels is related to the functional status of the AR in relation to the previously mentioned polymorphic CAG repeats within the AR genome.[39,41,42] If increased AR functional activity also resulted in increased PSA production, this could explain why serum PSA levels in black men (who have short CAG alleles) with or without a diagnosis of prostate cancer were higher in a number of recent studies, some of which controlled for prostate and tumor volume.[52,53]

## CONCLUSION

Black men are exposed to higher levels of circulating androgens from birth to approximately age 35 years (which predates the onset of clinical prostate cancer). Further, significant differences exist in 5α-reductase activity among the races, and these differences correlate with the subsequent risk for the development of prostate cancer. In addition, several racial/ethnic-specific genetic polymorphisms that could affect tissue DHT levels have been identified in the 5α-reductase type II gene and androgen receptor-inactivating mutations exist among latent carcinomas from Japanese, but not white patients. Finally, differences in genetic polymorphisms of the amino-terminal trinucleotide repeats (CAG, GGC) of the AR among races are significantly associated with the incidence and severity of prostate cancer.

Collectively, these data strongly suggest that

racial differences within the androgen/receptor pathway not only exist, but could be causally related to clinically observed differences in the biology of prostate cancer among the races.

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## Literature Cited

1. Landis SH, Murray J, Bolden S, Wingo PA. *Cancer Statistics.* 1999;49:8-31.

2. Pienta KJ. Etiology, epidemiology, and prevention of carcinoma of the prostate. In: Walsh PC, Retik AB, Vaughn ED, Wein AJ. *Campbell's Urology.* 7th ed. Philadelphia, PA: WB Saunders Co; 1998:2489-2496.

3. Mebane C, Gibbs T, Horm J. Current status of prostate cancer in North American black males. *J Natl Med Assoc.* 1990;82: 782-788.

4. Sakr WA, Grignon DJ, Haas GP, et al. Epidemiology of high grade prostate intraepithelial neoplasia. *Pathol Res Pract.* 1995; 191:838-841.

5. Wilson JD. Syndromes of androgen resistance. *Biol Reprod.* 1992;46:168-173.

6. Montie JE, Pienta KJ. Review of the role of androgenic hormones in the epidemiology of benign prostatic hyperplasia and prostate cancer. *Urology.* 1994;43:892-899.

7. McConnell JD. 5α-reductase inhibitor therapy: limitations and advances. In: Stamey TA, ed. *Monographs in Urology.* Monteverde, FL: Medical Directions Publishing Co; 1997:105-119.

8. Silver RI, Wiley EL, Thigpen AE, Guileyardo JM, McConnell JD, Russell DW. Cell type specific expression of steroid 5α-reductase 2. *J Urol.* 1994;152:438-442.

9. Young CYF, Montgomery BT, Andrews PE, Qiu S, Bilhartz DL, Tindall DJ. Hormonal regulation of prostate-specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. Cancer Res. 1991;51:3748-3752.

10. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res.* 1977;37:1929-1933.

11. Culig Z, Hobisch A, Cronauer MV, et al. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. *Mol Endocrinol.* 1993;7:1541-1550.

12. Grino PB, Griffin JE, Wilson JD. Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. *Endocrinology.* 1990;126:1165-1172.

13. O'Malley BW, Tsai M-J. Molecular pathways of steroid receptor action. *Biol Reprod.* 1992;46:163-167.

14. Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5α-reductase isozyme expression. *J Clin Invest.* 1993;92: 903-910.

15. Ghanadian R, Puah CM, O'Donoghue EPN. Serum testosterone and dihydrotestosterone in carcinoma of the prostate. *Br J Cancer.* 1979;39:696-699.

16. Ahluwalia B, Jackson MA, Jones GW, Williams AO, Mamidanna SR, Rajguru S. Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. *Cancer.* 1981;48:2267-2273.

17. Osegbe DN, Ogunlewe JO. Androgen concentration in blacks with benign and malignant prostatic disease. *J Urol.* 1988; 146:160-164.

18. de Jong FH, Oishi K, Hayes RB, et al. Peripheral hormone levels in controls and patients with prostatic cancer or benign prostate hyperplasia: results from the Dutch-Japanese case-control study. *Cancer Res.* 1991;51:3445-3550.

19. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res.* 1988;48:3515-3517.

20. Barrett-Connor E, Garland C, McPhillips JB, Khaw K, Wingard DL. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. *Cancer Res.* 1990;50:169-173.

21. Hsing AW, Comstock GW. Serological precursors of cancer: serum hormones and risk of subsequent prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 1993;2:27-32.

22. Henderson BE, Bernstein L, Ross RK, Depue RH, Judd HL. The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer.* 1988;57:216-218.

23. Ross R, Bernstein L, Judd H, Hanisch R, Pike M, Henderson B. Serum testosterone levels in healthy young black and white men. *J Natl Cancer Inst.* 1986;76:45-48.

24. Ellis L, Nyborg H. Racial/ethnic variations in male testosterone levels: a probable contributor to group differences in health. *Steroids.* 1992;57:72-75.

25. Ross RK, Bernstein L, Lobo RA, et al. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *Lancet.* 1992;339:887-889.

26. Lookinbill DP, Demers LM, Wang C, Leung A, Rittmaster RS, Santen RJ. Clinical and biochemical parameters of androgen action in normal healthy Caucasian versus Chinese subjects. *J Clin Endrocrinol Metab.* 1991;72:1242-1248.

27. Reichardt JKV, Makridakis N, Henderson BE, Yu MC, Pike MC, Ross RK. Genetic variability of the human SRD5A2 gene: implications for prostate cancer risk. *Cancer Res.* 1995;55: 3973-3975.

28. Makridakis N, Ross R, Pike MC, et al. A prevalent missense substitution that modulates activity of prostatic steroid 5α-reductase. *Cancer Res.* 1997;57:1020-1022.

29. Brown TR. Provocative aspects of androgen genetics. *Prostate.* 1996;6:9-12.

30. Newmark JR, Hardy DO, Tonb DC, et al. Androgen receptor gene mutations in human prostate cancer. *Proc Natl Acad Sci USA.* 1992;89:6319-6323.

31. Gaddipati JP, McLeod DG, Heidenberg HB, et al. Frequent detection of codon 877 mutations in the androgen receptor gene in advanced prostate cancers. *Cancer Res.* 1994;54:2861-2864.

32. Brawn PN, Johnson EH, Kuhl DL, et al. Stage at presentation and survival of white and black patients with prostate carcinoma. *Cancer.* 1993;71:2569-2573.

33. Optenberg SC, Thompson IM, Friedrichs P, Wojcik B, Stein CR, Kramer B. Race, treatment, and long-term survival from prostate cancer in an equal access medical care delivery system. *JAMA.* 1995;274:1599-1605.

34. Fowler JE, Bigler SA, Renfroe DL, Dabagia MD. Prostate specific antigen in black and white men after hormonal therapies for prostate cancer. *J Urol.* 1997;158:150-154.

35. Takahashi H, Furusato M, Allsbrook WC, Nishii H, Wakui

S, Barrett C. Prevalence of androgen receptor gene mutations in latent prostatic carcinomas from Japanese men. *Cancer Res.* 1995;55:1621-1624.

36. Sadi MV, Walsh PC, Barrack ER. Immunohistochemical study of androgen receptors in metastatic prostate cancer: comparison of receptor content and response to hormonal therapy. *Cancer.* 1991;67:3057-3064.

37. Sadi MV, Barrack EV. Image analysis of androgen receptor immunostaining in metastatic prostate cancer. *Cancer.* 1993; 71:2574-2580.

38. Edwards A, Hammond HA, Jin L, Caskey CT, Chakraborty R. Genetic variation at five trimeric and tetrameric tandem repeats loci in four human population groups. *Genomics.* 1992;12: 241-253.

39. Hakimi JM, Schoenberg MP, Rondinelli RH, Piantadosi S, Barrack ER. Androgen receptor variants with short glutamine and glycine repeats may identify unique subpopulations of men with prostate cancer. *Clin Cancer Res.* 1997;3:1599-1608.

40. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acids Res.* 1994;22:3181-3186.

41. Irvine RA, Yu MC, Ross RK, Coetzee GA. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res.* 1995;55: 1937-1940.

42. Giovannucci E, Stampfer M, Krithivas K, et al. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc Natl Acad Sci USA.* 1997;94:3320-3323.

43. Partin AW, Oesterling JE. The clinical usefulness of prostate specific antigen: update 1994. *J Urol.* 1994;152:1358-1368.

44. Babaian RJ, Troncoso P, Steelhammer LC, Loreta-Trull J, Ramirez EI. Tumor volume and prostate specific antigen: implications for early detection and defining a window of curability. *J Urol.* 1995;154:1808-1812.

45. Pettaway CA, Pathak S, Green G, et al. Selection of highly metastatic variants of human prostatic carcinomas (PC-3M, LNCaP) utilizing orthotopic implantation in nude mice. *Clin Cancer Res.* 1996;2:1627-1636.

46. Hsieh JT, Wu HC, Gleave ME, von Eschenbach AC, Chung LWK. Autocrine regulation of prostate specific antigen gene expression in a human prostate cancer (LNCaP) cell line. *Cancer Res.* 1993;53:2852-2857.

47. Vijayakumar S, Karrison T, Weichselbaum RR, Chan S, Quadri SF, Awan AM. Racial differences in prostate-specific antigen levels in patients with local-regional prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 1992;1:541-545.

48. Moul JD, Sesterhenn IA, Connelly RR, et al. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. *JAMA.* 1995;274:1277-1281.

49. Morgan TO, Jacobsen SJ, McCarthy WF, Jacobsen DJ, McLeod DG, Moul JW. Age-specific reference ranges for serum prostate-specific antigen in black men. *N Engl J Med.* 1996;335: 304-310.

50. Oesterling JE, Kumamoto Y, Tsukamoto T, et al. Serum prostate specific antigen in a community-based population of healthy Japanese men: lower values than for similarly aged white men. *Br J Urol.* 1995;75:347-353.

51. Powell IJ, Heilbrun LK, Sakr W, et al. The predictive value of race as a clinical prognostic factor among patients with clinically localized prostate cancer: a multivariate analysis of positive surgical margins. *Urology.* 1997;49:726-731.

52. Henderson RJ, Eastham JA, Culkin DJ, et al. Prostate-specific antigen (PSA) and PSA density: racial differences in men without prostate cancer. *J Natl Cancer Inst.* 1997;89:134-138.

53. Pettaway CA, Troncoso P, Ramirez EI, Johnston D, Steelhammer L, Babaian RJ. Prostate specific antigen and pathological features of prostate cancer in black and white patients: a comparative study based on radical prostatectomy specimens. *J Urol.* 1998; 160:437-442.

54. Vijayakumar S, Quadri SF, Dong L, et al. Results of a study to correlate serum prostate specific antigen and reproductive hormone levels in patients with localized prostate cancer. *J Natl Med Assoc.* 1995;87:813-819.