PROSTATE-SPECIFIC ANTIGEN AND ANDROGENS IN AFRICAN-AMERICAN AND WHITE NORMAL SUBJECTS AND PROSTATE CANCER PATIENTS

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Prostate cancer in African Americans is more aggressive and common than in any other racial group. An endocrine mechanism has been proposed to account for this racial difference. However, androgen levels in African-American elderly normal subjects and prostate cancer patients have been insufficiently studied. Because the Albert Einstein Medical Center (AEMC) has a large African-American population, we could contribute racial data from which observations could be made within this study and in past and future studies.

Blood from 38 screened men (mean age 65) with prostate-specific antigen (PSA) less than 4 ng/mL and normal rectal examination seen at the AEMC Cancer Center was studied using standard radioimmunoassays. The blood samples also served as our control. Our experimental group consisted of 51 prostate cancer patients (mean age 71 years), all of whom had nonmetastatic prostate cancer. Subjects were categorized by cancer status, race, and age group.

In our screened subjects, PSA, testosterone, and dihydrotestosterone were not higher in African Americans than in whites. Furthermore, our prostate cancer patients demonstrated no significant racial variation for PSA, testosterone, and dihydrotestosterone. Our data also did not indicate any correlation between PSA and androgen levels in our cancer patients.

In our population of elderly men, no racial differences in androgen levels were found. Androgen levels did not correlate with PSA levels in prostate cancer patients. (*J Natl Med Assoc.* 2000;92:445–449.)

Key words: prostate cancer ♦ African Americans ♦ androgen ♦ antigen

Only age, race, and high dietary fat have consistently been found to be risk factors for cancer of the prostate. However, androgens have been implicated in its induction, growth, and maintenance. Supporting these roles are:

1. The development of prostate cancer in rats experimentally following prolonged administration of testosterone (T).
2. The absence of cancer of the prostate in men who had prepubertal orchiectomy.
3. The low incidence of cancer of the prostate in persons with high levels of estrogens.
4. The high levels of circulating androgens (and androgen receptors) found in neoplastic prostatic tissues.

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5. The regression of cancer following ablative or antiandrogen therapy.[1]

Testosterone is secreted by the testicular Leydig cell mainly in response to luteinizing hormone from the pituitary gland. In the prostate, testosterone is converted via the enzyme, type 2,5-α-reductase, to the more potent androgen, dihydrotestosterone (DHT). Both T and DHT play crucial roles in the proliferation and maintenance of prostatic tissue, whether benign or malignant.[2,3] Consequently, many studies have sought to examine whether T and DHT levels could serve as prognostic indicators for the development of prostate cancer. Clinically there has been controversy concerning T and DHT levels in untreated cancer patients. Investigators studying T and DHT levels have found equivocal results in examining these androgens. Nonetheless, much of the data suggests that androgens are not responsible for the initiation of prostate cancer but still may facilitate progression of the cancer. It should be noted, however, that many of these studies examined whites and failed to include African Americans.

African Americans develop cancer of the prostate more frequently and aggressively than do whites for reasons that are poorly understood.[4–6] Prostate-specific antigen (PSA) has been reported to be higher in African Americans than in whites, yet its basis is still not fully understood.[7–9] It has been suggested that an endocrine mechanism could account for the aggressive nature of prostate cancer after its initiation in African Americans. Some investigators found elevated androgen levels in African Americans compared with whites.[10,11] However, other investigators reported no significant difference in androgen levels between African Americans and whites.[5,9,12,13] Clearly, T and DHT levels in aging white and African-American men, especially with cancer of the prostate, must be further investigated with sufficient numbers for significant statistical analyses. In addition, if any subsequent correlation is found, additional investigations would be needed to confirm whether these androgens could possibly account for the more rapid progression of this cancer in African Americans.

Therefore, we wanted to determine and compare male hormone levels in African-American and white elderly males without evidence of prostate cancer and with localized cancer and correlate PSA with pretreatment androgen levels.

MATERIALS AND METHODS

From February 1993 to June 1994, any patient with prostate cancer seen at the Radiation Oncology Department at the Albert Einstein Medical Center who was willing to sign an institutional review board (IRB) approval consent had blood drawn and quickly frozen for later assessment of T, DHT, and PSA. In addition, any patient greater than 55 years old screened at the Cancer Center with normal PSA and rectal examination who was willing to sign an IRB approval consent had blood withdrawn and quickly frozen for the later assessment of T, DHT, and PSA.

There were 51 prostate cancer patients with an average age of 71 years who were seen for an initial evaluation. All cancer patients had nonmetastatic prostate cancer. The 33 African Americans had a mean age of 70 years, whereas the 18 whites had a mean age of 73 years. From PSA screenings, 38 elderly men (12 African Americans and 26 whites) served as our control.

Subjects were categorized by cancer status (screened subjects compared to cancer patients), race (African American compared to white), and age group (stratified by decade). Because elderly subjects are known to have decreased circadian variation in hormone levels, the time of day at which the blood was drawn was not considered. Furthermore, no corrections were made for any seasonal variations.

Total T levels were measured by radioimmunoassay (RIA) using the coated tube (antibody) method (Diagnostic System Laboratories, Webster, TX). The sensitivity of the test is 0.1 ng/mL (distinguishable from 0 at the 95% confidence limit), with intra-assay coefficient of variation (CV) of less than 8%. The cross-reactivity is 6% with DHT, 2% with 5α-androstenediol, and less than 1% with all other androgens. Therefore, the test was carried out directly on the serum sample. Published normal values for the elderly range between 0 and 9 ng/mL with a mean of 4.[1,14,15]

DHT was assayed by RIA (Amersham Life Science, Arlington Heights, IL) initially with [^{3}H]DHT as the tracer and later with I-125 label (Diagnostic System Laboratories), using the dextran-coated charcoal method for separation of the free and antibody-bound ligand. The serum sample was extracted with ether. The ether phase was evaporated to dryness and then redissolved in buffer. At this stage, the sample was treated with oxidizing agent

($KMnO_4$) to destroy T, leaving DHT intact. With this method, separation of the cross-reacting species by chromatography was unnecessary. The sample was again extracted with ether, evaporated, and redissolved as above. Procedural loses were monitored by the addition of a small amount of [^{3}H]DHT to the test sample. Recovery rates were 80%–90%, and the results were corrected for dilution and losses by this method. The sensitivity of the assay is 0.125 ng/mL, with an intra-assay CV of 5%. The cross-reactivity is 7% with 5α-androstanediol, 2% with androstanedione, and less than 1% with other hormones. The only published normal values we could find were exclusively either for whites (0.1 to 0.9 with a mean of 0.5) or for younger men (0.49 to 1.34).[1,14]

PSA levels were determined by microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). The sensitivity of the assay was 0.2 ng/mL, with an intra-assay CV of 3%. Normal values for healthy males were between 0 and 4 ng/mL (with 0.3% of subjects under 40 years showing values between 4 and 10 ng/mL, and 1.3% over 40 years showing values between 4 and 30 ng/mL, with 40%–80% of cancer patients in this range depending on disease stage).

Clinical staging for all localized prostate cancer patients before treatment included chest x-ray, CT scan of the abdomen and pelvis, bone scan, PSA, bilirubin-urea-nitrogen, and alkaline phosphatase. Excluding 31 patients whose treatment was not limited to curative x-ray tomography (XRT) alone, the stages were Jewett and Strong's stages A & B, T1&T2N0M0 (prostate carcinoma stage I and II: tumor not more than 5 cm in its greatest dimension [T1 & T2], no regional lymph node metastasis [N0], no distant metastasis [M0]), for 40 patients pre-XRT and 48 post-XRT and T3&T4N0M0 (III, IV or Jewett and Strong C, D) for 11 pre-XRT and 11 post-XRT. T1N0M0 represented 16.4%; T2N0M0, 63.6%. T3N0M0 represented 20% and T4N0M0 3% of the latter patients. There were 12 pre-XRT and 21 post-XRT patients who had Gleason scores ranging from 2 to 4. Gleason scores of 5 to 7 were seen in 32 pre-XRT and 33 post-XRT patients, whereas scores ranging from 8 to 10 corresponded with 7 pre-XRT and 5 post-XRT patients. Unfortunately, all desired tests could not be performed on all patients because of insufficient material.

Subjects were categorized by treatment status (screened subjects compared to pre-XRT vs. post-XRT), race (African American compared to white), age group (stratified by decade), Gleason score (2 to 4, 5 to 7, and 8 to 10), and Jewett and Strong clinical stage (A, B, C, and D). Treated patients were divided into subgroups of less than or more than 1 year post-XRT. Because elderly subjects are known to have decreased circadian variation in hormone levels, the time of day at which the blood was drawn was not considered. Furthermore, no corrections were made for any seasonal variations.

Statistical methods included analysis of variance (ANOVA), unpaired t tests, Mann-Whitney U tests, and Pearson and Spearman correlations. First we determined if the data in each condition were distributed normally. We transformed any skewed data using the natural log. The data were subsequently analyzed using parametric tests. If, despite our correlation, the data remained skewed, nonparametric testing was utilized. Within each group and race, Pearson and Spearman correlations between age and laboratory values for PSA, T, and DHT were performed. Furthermore, a 2-factor ANOVA by age and race within both categories was performed to determine any main effect of age or age-race interaction. When the results indicated that age was relevant, it was included in a 3-factor ANOVA. Otherwise, a 2-factor ANOVA for each of the laboratory values by race and cancer status was performed. Finally, Pearson and Spearman correlations were used to relate PSA with T or DHT within the cancer group. We did not perform these correlations in our screened subjects due to this group's small sample size.

RESULTS

For both our screened subjects and cancer patients, no significant racial discrepancy in PSA levels was found. Comparisons of PSA levels by race and cancer status are shown in Table 1. More details are provided in the corresponding sections below.

Total Testosterone

Mean total T with both our screened subjects and cancer patients was within the published normal range. However, it was found to be significantly higher ($p < 0.05$) in screened whites (4.10 ng/mL) than in African Americans (3.30 ng/mL). This significant racial difference was not found in our cancer patients. However, in our cancer patients as a whole, T levels (5.61 ng/mL) were elevated ($p < 0.05$) when compared with our screened subjects (3.85 ng/mL). This same trend was observed in

Table 1. Age, T, DHT, and PSA by Race in Screened Subjects and Prostate Cancer Patients

Patient Type	Race*	No. of Pts.	Mean Age (years)	No. of Pts.	Mean T (ng/mL)	No. of Pts.	Mean DHT (ng/mL)	No. of Pts.	Geometric Mean of PSA (ng/mL)
Screened subjects									
Total		38	65	36	3.85	36	0.40	38	0.88
	AA	12	63	10	3.30	10	0.33	12	0.80
	W	26	66	26	4.10	26	0.43	26	0.91
Cancer patients									
Total		51	71	43	5.61	51	1.13	51	11.16
	AA	33	70	27	5.82	33	1.10	33	12.24
	W	18	73	16	5.26	18	1.18	18	9.42

*AA, African American; W, white.

comparison of our cancer patients with screened subjects in both of the respective racial groups. Lastly, we found no correlation between T levels and PSA in our cancer patients. Comparisons of T levels for both study groups are also shown in Table 1.

Dihydrotestosterone

In screened subjects, DHT was noted to be significantly higher ($p < 0.05$) in whites (0.43 ng/mL) than in African Americans (0.33 ng/mL), but both were within the published normal 95% confidence interval. No significant racial difference was apparent within the cancer patient group. As a whole, the cancer group demonstrated significantly elevated levels of DHT (1.13 ng/mL, $p < 0.05$) when compared with screened subjects (0.40 ng/mL). Furthermore the same trend was evident for both of the respective racial groups as well. Finally, values of DHT did not correlate with PSA in prostate cancer patients. Comparisons of DHT levels for the two study groups are also shown in Table 1.

DISCUSSION

Androgen levels with their hypothalamic-pituitary-associated hormones in elderly normal males and prostatic carcinoma patients have not been fully classified. There is a failure to clearly elucidate a profile of expected values for the elderly, let alone the elderly African-American male. High, normal, and low levels of T and DHT have been reported at the time of diagnosis of varying stages of prostate cancer. Much of the published data either fails to mention racial distribution or lacks sufficient numbers of African Americans to reflect the racially mixed populations of large eastern U.S. cities, where African Americans represent 10%–40% of the patients.[16–18] Moreover, most publications also fail to indicate age groups they studied. Only recently has PSA in African-American men been thoroughly studied and compared with whites. Unfortunately, however, the analysis of both normal and prostate cancer patients frequently does not include accompanying hormone levels.[6,19] Thus, we chose to measure androgen levels and PSA in African-American and white elderly men from screening who were deemed clinically and biochemically normal and compare these results with those of our prostate cancer patients.

Previous studies comparing T levels in African Americans and whites have not provided definitive results. Ross et al.[10] noted that African-American men in college had 15% higher T levels than did whites of similar age. Ellis et al.[11] reported a similar finding in older-aged subjects, though with results not as substantial. Conversely, some later studies, one of which was conducted by Ross, recorded no significant difference in T levels between white and African-American men.[5,9,12,13] However, our study failed to corroborate these past studies. In fact, our elderly white-screened subjects had higher T levels than did screened African Americans. But in our cancer patients, we noted no significant racial variation for T levels. This finding is consistent with a study by Vijayakumar et al.,[12] which found no significant discrepancy in T levels for African-American and white cancer patients with a mean age of 70.

DHT has been poorly studied in the past probably due to the lack, until recently, of a simple RIA technique. Our screened white subjects had higher DHT levels than did screened African-American subjects. In comparison, Wu et al.[13] reported that

elderly healthy African-Americans had significantly higher DHT levels than did comparable whites. Unlike our screened subjects, we observed no difference between the races for DHT levels in our cancer patients. In addition, the cancer group had levels of DHT that were higher than DHT levels in screened subjects. We cannot, however, compare these values with any published standard, because none has the appropriate age and racial distribution.

The relationships and possible prognostic value of various androgen levels in patients with prostate cancer have been studied with conflicting results for various reasons. The literature fails to report values of T and DHT for elderly African-Americans males with or without prostate carcinoma. Our data provides some baseline values for African Americans and whites from which comparisons can be made within this study as well as within previously published studies and in future studies.

Heavy alcohol consumption and certain commonly prescribed medications can contribute to changes in measured androgen levels. We did not include these factors in our analysis.

In summary, African Americans in our elderly population did not have elevated androgen levels in comparison with whites. This finding is not consistent with the results reported by Ross et al.[10] and Ellis et al.[11] in a younger population of normal subjects. Furthermore, we did not find any correlation between PSA and androgen levels in our cancer patients. Therefore, differences in androgen levels may not be the putative cause of higher PSA levels among African Americans compared with whites[7,8,20–22] in the United States.

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