

Abnormal Levels of Plasma Hormones in Men With Prostate Cancer: Evidence Toward a “Two-Disease” Theory

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The 24-hr mean plasma concentrations of 13 hormones or hormone metabolites (cortisol, testosterone, dihydrotestosterone, dehydroisoandrosterone, dehydroisoandrosterone sulfate, androsterone, androsterone sulfate, estrone, thyroxine, triiodothyronine, LH, FSH, and prolactin) were measured in 16 rigorously screened patients (aged 55–80) with stage C or D prostate cancer and 36 normal men. Nine of the hormones showed no abnormalities in the patients but four (testosterone, dihydrotestosterone, cortisol, and estrone) showed abnormalities. Testosterone and dihydrotestosterone, which, respectively, decreased with age and showed no change with age in the normal men, *rose* sharply with age in the patients. The patients' curves crossed the normal curves at about age 65; patients 65 or above showed normal values while patients under age 65 showed significantly subnormal levels of both hormones: testosterone averaged 282 ng/dl in patients vs 434 ng/dl in controls ($P < 0.0001$) and dihydrotestosterone averaged 70 ng/dl in patients vs 99 ng/dl in controls ($P < 0.01$). Cortisol, which was age invariant in the normal men, *fell* sharply with age in the patients; patients under 65 had significantly elevated levels (10.1 vs 6.9 $\mu\text{g/dl}$; $P < 0.0001$), while patients 65 or older had normal levels. Estrone levels were age invariant in both patients and controls, but the mean level in patients was markedly elevated (81 vs 47 pg/ml in controls; $P < 0.001$). The cortisol/testosterone ratio almost completely separated prostate cancer patients under 65 from normal men, but did not discriminate patients 65 or older from normal.

The findings indicate that prostate cancer patients under 65 differ markedly in their endogenous hormonal pattern from patients 65 or older. This leads us to propose a “two-disease” theory of prostate cancer, with possible differences in genetic factors and prognosis.

Key words: prostate cancer; plasma hormones; testosterone; cortisol; estrone; age effects

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INTRODUCTION

The clear-cut hormone dependence and hormone responsiveness of prostate cancer have stimulated extensive study of the endogenous hormonal environment of men with this disease. One group has described elevated plasma cortisol levels [1,2], and there have been scattered, inconsistent, and unremarkable findings about the levels of several other plasma hormones [3–9], but most of the recent interest has focused on plasma testosterone levels: Six studies [3–8] have reported subnormal levels in some patients and normal levels in others, while seven studies [9–15] have reported only normal levels; none has reported elevated levels. The present senior author has reviewed these studies in detail [16].

In this study we measured the 24-hr mean plasma concentrations of 13 hormones (cortisol, testosterone, dihydrotestosterone, dehydroisoandrosterone (DHA), dehydroisoandrosterone sulfate (DHAS), androsterone, androsterone sulfate, estrone, triiodothyronine (T3), thyroxine (T4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin) in 16 rigorously screened and uncomplicated prostate cancer patients aged 55 to 80 and 36 normal men aged 21 to 85. The cancer patients showed abnormal levels of four hormones, and for three of these the abnormalities were highly age-dependent.

METHODS

Patients and Normal Subjects

The patients were men with previously untreated stage C or D prostate cancer; the normal subjects were carefully screened to rule out any factors known or suspected to alter endocrine function (eg, medications, current or past major illness, history of hormonal therapy of any kind, obesity, etc), and all gave informed consent for the study.

The 24-hr Mean Plasma Hormone Concentration

Small samples of blood were drawn from an indwelling venous catheter every 20 min for 24 hr, as previously described from this laboratory [17]. Aliquots of plasma from each sample were pooled, and the concentrations of the hormones studied were measured in the pool, to yield the 24-hr mean concentrations.

Hormone Determinations

Cortisol was determined by the standard protein-binding method [18]. Testosterone and dihydrotestosterone were determined by radioimmunoassay with a single antibody, after chromatographic separation of the two steroids in the plasma extract, as previously reported from this laboratory [19]. Estrone was determined by radioimmunoassay, as described from this laboratory [20]. All the other hormones were determined by standard radioimmunoassay methods described in the literature.

STATISTICAL METHODS

The significances of intergroup differences in mean hormonal concentrations were calculated by the application of Student's *t*-test, two-tailed, to the log-transformed

data. The significances of various correlations of age vs hormone concentration were calculated by means of Pearson's r .

RESULTS

Plasma Testosterone

There was a significant downward slope of the age vs concentration curve in the normal controls as we [21] and others [22] have recently reported; in striking contrast, the curve in the cancer patients showed a highly significant *upward* slope ($r = 0.68$, $P < 0.01$) (Fig. 1). The patients' curve crossed the normal curve at about age 65. A scattergram of the data (Fig. 2) showed that the patients under 65 had substantially lower values than the normal controls (282 vs 434 ng/dl, $P < 0.0001$), while the patients 65 or over had essentially normal values.

The small errors introduced into this comparison by neglecting the difference in mean age between the under 65 patients (60.1) and the control group (42.6) or between the over 65 group (71.1) and the control group are essentially negligible, since the normal testosterone level declines by only 4.3 ng/dl per year of age; it has, therefore, been ignored for purposes of simplifying the analysis. If it were corrected for, the difference between under 65 patients and controls would decrease by 75 ng/dl but would still be highly significant, while the difference between over 65 patients and controls would change from -2 ng/dl to $+41$ ng/dl and would still be nonsignificant.

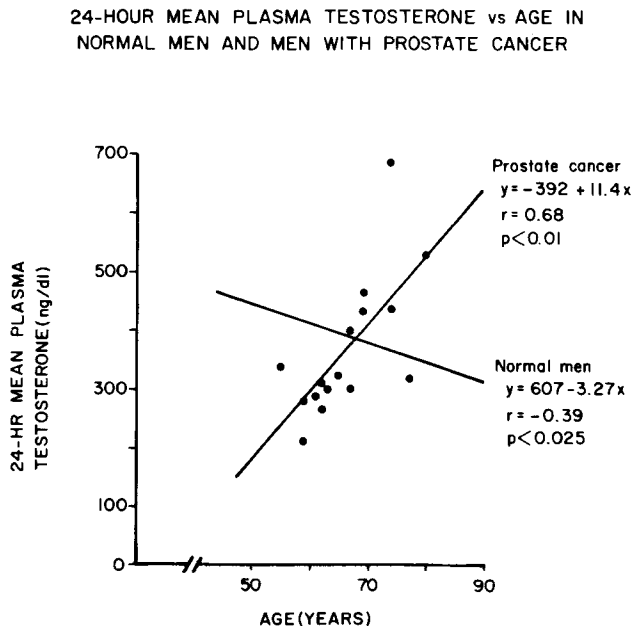


Fig. 1. Relationship of 24-hr mean plasma testosterone concentration to age in normal men and men with prostate cancer. The concentration declined with age in normals and rose with age in patients.

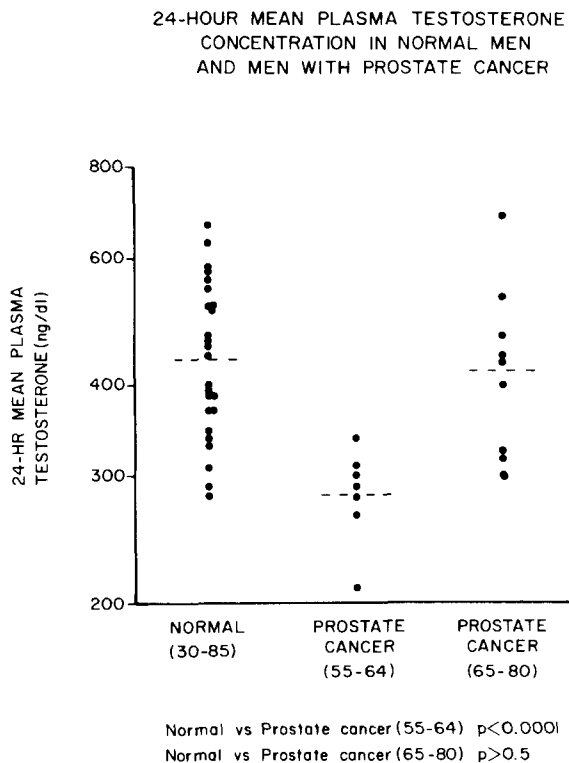


Fig. 2. The 24-hr mean plasma testosterone in normal men and patients with prostate cancer. Patients under 65 had significantly subnormal levels, while those 65 or above had normal levels.

Plasma Dihydrotestosterone

As with testosterone, the level of dihydrotestosterone was subnormal in the patients under 65 (70 vs 99 ng/dl, $P < 0.01$) and was essentially normal in patients 65 or over (Fig. 3).

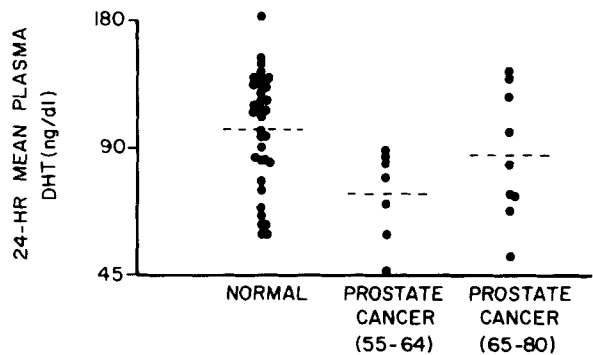
Plasma Cortisol

Plasma cortisol concentration was age invariant in the normal subjects but showed a definite downward slope ($r = -0.44$, $P = 0.06$) in the prostate cancer patients (Fig. 4). A scattergram showed that patients under 65 had very significantly elevated cortisol levels (10.1 vs 6.9 $\mu\text{g/dl}$, $P < 0.0001$) while patients 65 or older had essentially normal levels (Fig. 5).

Plasma Estrone

Plasma estrone concentration was age invariant in both the normal subjects and the prostate cancer patients. The values in the cancer patients were markedly higher (81 vs 47 pg/ml, $P < 0.001$) (Fig. 6).

24-HOUR MEAN PLASMA DIHYDROTESTOSTERONE IN
NORMAL MEN AND MEN WITH PROSTATE CANCER



Normal vs Prostate cancer (55-64) $p < 0.01$

Normal vs Prostate cancer (65-80) $p = \text{N.S.}$

Fig. 3. The 24-hr mean plasma dihydrotestosterone in normal men and patients with prostate cancer. Patients under 65 had significantly subnormal levels, while those 65 or above had normal levels.

RELATIONSHIP OF PLASMA CORTISOL TO AGE
IN NORMAL MEN AND MEN WITH PROSTATE CANCER

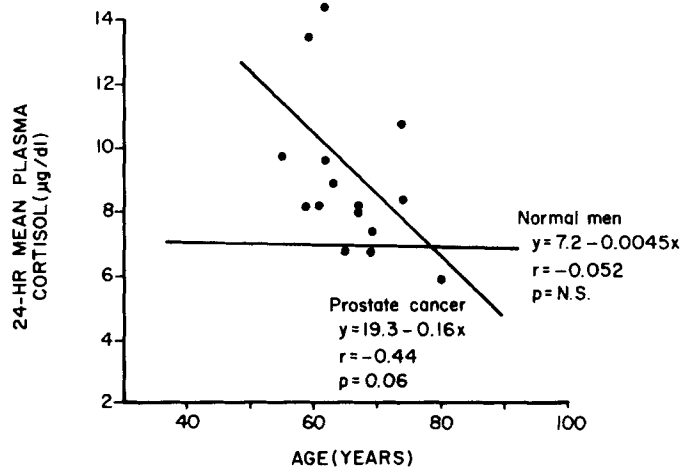


Fig. 4. Relationship of the 24-hr mean plasma cortisol concentration to age in normal men and men with prostate cancer. The concentration was age invariant in normal men and fell with age in patients.

24-HOUR MEAN PLASMA CORTISOL CONCENTRATION IN
NORMAL MEN AND MEN WITH PROSTATE CANCER

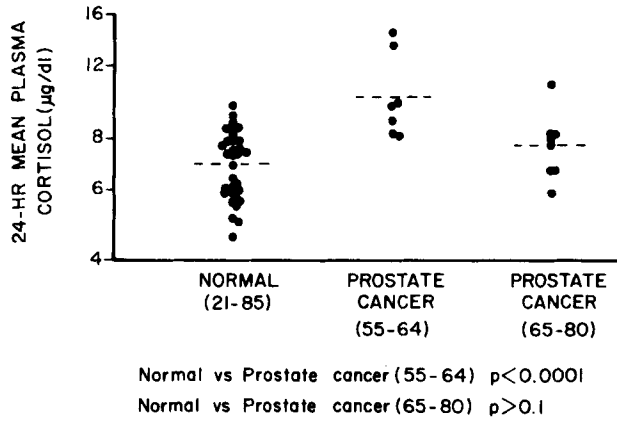


Fig. 5. The 24-hr mean plasma cortisol in normal men and men patients with prostate cancer. Patients under 65 had significantly elevated levels, while those 65 or above had normal levels.

24-HOUR MEAN PLASMA ESTRONE
CONCENTRATION IN NORMAL MEN
AND MEN WITH PROSTATE CANCER

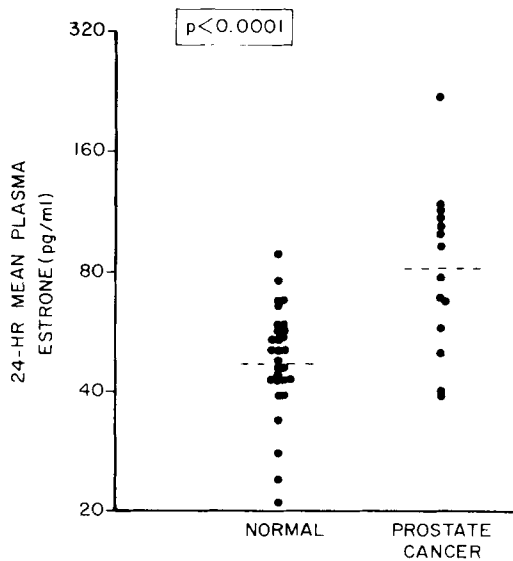


Fig. 6. The 24-hr mean plasma estrone in normal men and men with prostate cancer.

Plasma Testosterone/Cortisol Ratio

The plasma levels of four hormones-testosterone, dihydrotestosterone, cortisol, and estrone-were found to be abnormal in the prostate cancer patients we studied; the pletely separated prostate cancer patients under 65 from normal men (Fig. 8), while patients 65 and older were indistinguishable from normal men.

Other Hormones

The patients and controls did not differ significantly with respect to the plasma concentrations of the other nine hormones measured (DHA, DHAS, androsterone, androsterone sulfate, T3, T4, LH, FSH, and prolactin).

DISCUSSION

The plasma levels of four hormones-testosterone, dihydrotestosterone, cortisol, and estrone-were found to be abnormal in the prostate cancer patients we studied; the first two were subnormal and the second two were elevated. All these abnormalities have been reported separately before, but our present finding of a striking relationship of three of the abnormalities to the age of the patient has not. Whereas the plasma levels of testosterone declined with age and those of dihydrotestosterone and cortisol

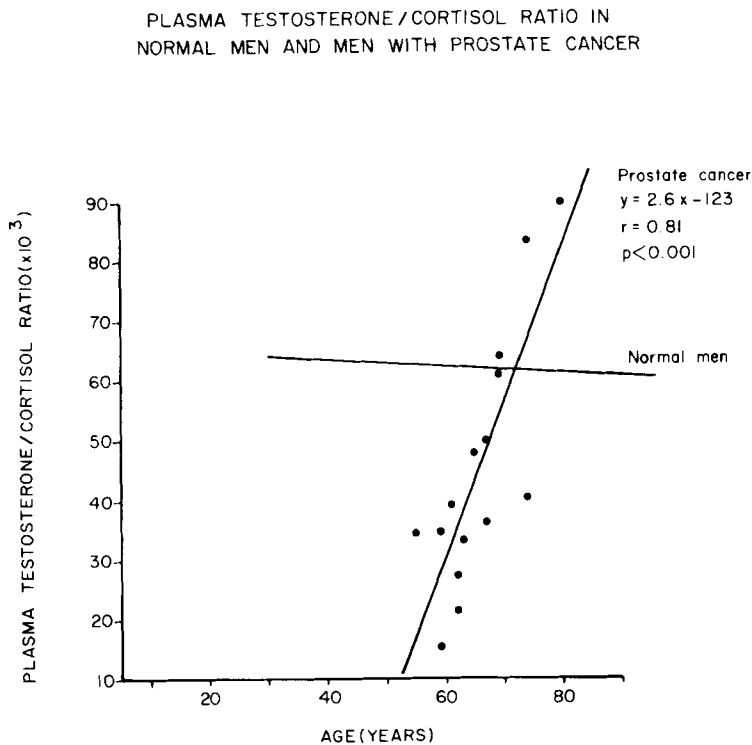


Fig. 7. Relationship of the 24-hr mean plasma testosterone/cortisol ratio to age in normal men and men with prostate cancer. The ratio fell slightly with age in normals and rose sharply with age in patients.

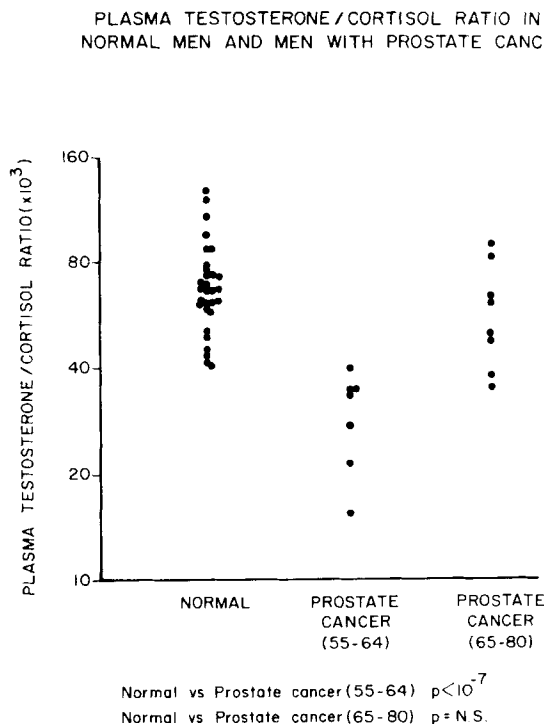


Fig. 8. The 24-hr mean plasma testosterone/cortisol ratio in normal men and patients with prostate cancer. The range of values for patients under 65 was much lower than that of normals, with no overlap; patients 65 or above did not differ significantly from normal.

were age invariant in the normal men we studied, the prostate cancer patients showed a sharp *upward* slope of the first two with age and a sharp *downward* slope of the third. Patients under 65 had highly significant depressions of plasma testosterone and dihydrotestosterone and highly significant elevations of plasma cortisol, while patients 65 or older had normal values of all three. The testosterone/cortisol ratio almost completely separated all the under 65 cancer patients from all the normals, but did not significantly discriminate patients 65 or older from normal.

Our findings indicate that prostate cancer patients younger than 65 differ markedly in their endogenous hormonal pattern from patients 65 or older. This leads us to propose a "two-disease" theory of prostate cancer analogous to the "two-disease" theory of breast cancer that has been proposed by several workers [23,24]. In the case of breast cancer, the "two diseases" differ in geographic distribution, relation to diet, and genetic risk [25-27], and hormonally, in that premenopausal patients have subnormal production of adrenal androgens while postmenopausal patients do not [28,29]; in the case of prostate cancer, in addition to the hormonal dichotomy, we have found that younger patients have a significantly poorer prognosis [30], and very recent studies have suggested that they may have a more definite genetic risk than older patients [31]. It is of interest that Doe's group [1,2] reported poorer prognosis in prostate cancer patients with higher plasma cortisol levels, but unfortunately they did not report the ages

of their patients so it is not clear whether they were really observing parallel "two-disease" dichotomies in hormonal milieu, age, and prognosis.

Though our hypothesis is clearly speculative at this point, we feel that further investigation and, we hope, confirmation may offer a fresh perspective on the natural history of prostate cancer. This, in turn, may lead to improved prevention and/or treatment.

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