Peripheral Hormone Levels in Controls and Patients with Prostatic Cancer or Benign Prostatic Hyperplasia: Results from the Dutch-Japanese Case-Control Study


ABSTRACT

The possible relationship between changes in peripheral hormone levels and the occurrence of prostatic pathology was studied in a case-control study, involving estimation of various plasma hormones in 368 Dutch and 258 Japanese men, who were grouped as controls and patients with benign prostatic hyperplasia, focal prostatic carcinoma, or clinically evident prostatic carcinoma. Results of a number of previous, smaller studies concerning interrelationships between hormone levels in elderly men were confirmed within the Dutch and Japanese groups. Plasma levels of testosterone and estradiol were significantly lower in the Japanese men, when compared with those in Dutch men. Probably as a result of this difference in testosterone levels, the ratio between serum levels of dihydrotestosterone and testosterone was increased.

These differences were also found when results from Japanese subgroups (controls and patients with prostate pathology) were compared with those from the Dutch subgroups. There were no significant differences in plasma androgen levels between Japanese or Dutch prostate cancer cases and their respective control subgroups. These findings do not support a correlation between the lower plasma testosterone levels and a lower incidence of prostate cancer in the Japanese men.

Furthermore, no significant differences were found between salivary levels of testosterone or the ratio between testosterone and SHBG in the various Dutch subgroups. In Japanese benign prostatic hyperplasia patients, the testosterone to SHBG ratio was significantly increased.

In conclusion, the results of this retrospective, cross-sectional study do not indicate that hormonal levels play a primary role in the origin or promotion of prostatic abnormalities. The finding of a lower plasma testosterone in the Japanese men, however, remains suggestive, warranting a more extensive prospective study.

INTRODUCTION

Androgens have been implicated indirectly as being involved in the genesis of prostatic cancer, since tumors of the prostate have not been observed in eunuchs (see Ref. 1 for review). Similarly, cirrhosis of the liver, a condition known to increase peripheral estradiol levels, seems to lower the incidence of prostate cancer (2, 3).

A number of retrospective studies, in which possible anomalies of hormone levels in patients with prostate cancer were investigated, have been reported. In some of these investigations, patients with BPH3 were also included, because this condition has been considered a precursor lesion of prostate cancer by some authors (4). However, this point has been challenged by others (5), especially because the anatomical localization of BPH and prostate cancer suggests that these conditions originate from embryologically different parts of the prostate.

In a few of these studies, BPH patients were found to have increased levels of testosterone (6) or DHT (6, 7). In patients with cancer of the prostate, significant increases of peripheral levels of androgens were reported by Drafta et al. (8), but Bartsch et al. (9) found significantly decreased levels of testosterone and DHT in these patients. In the same groups of patients, relatively low levels of luteinizing hormone were observed (BPH: Refs. 10 and 11; prostate cancer: Refs. 9 and 11). This observation might indicate that higher levels of free steroids prevent the increase in luteinizing hormone levels, which is normally seen in older men, in BPH and prostate cancer patients. However, this explanation contrasts with the finding that the concentration of SHBG in plasma from BPH or prostate cancer patients was reported to be higher than or equal to that in nonafflicted controls (6, 12–14). No significant changes in the level of peripheral estradiol were found in patients with prostate cancer (12, 15). Finally, results of two prospective studies of hormone levels in prostatic carcinoma patients were published recently (16, 17). The only significant correlation between the occurrence of the disease and hormone levels was that of increased androstenedione levels (17).

From these data, no definite conclusions regarding hormonal abnormalities in patients with prostate cancer can be drawn. This may be due partly to the relatively small numbers of patients and controls studied and to factors which are intrinsically difficult to interpret, i.e., diurnal variation, influence of disease-related stress, and age-related changes. For these reasons, we decided to estimate parameters for the exposure of the prostate to androgens in large groups of control subjects and patients with prostatic cancer or BPH in two countries, the Netherlands and Japan (18), with a striking difference in the occurrence of prostatic cancer.

MATERIALS AND METHODS

Study Subjects. Between 1982 and 1985 a study of prostatic cancer and benign prostatic hyperplasia was carried out in the Rotterdam region of the Netherlands and in Kyoto, Japan, as part of a "Dutch-Japanese Case Control Study on Prostatic Cancer." Cases of prostatic cancer and of BPH were identified from the Departments of Urology at the hospitals of the Erasmus University Rotterdam, The Netherlands, and Kyoto University, Japan, and from a number of participating local hospitals. Controls were identified from patients hospitalized for minor surgical interventions in the Departments of Pulmonology, Orthopedics, E.N.T., and Surgery as previously described for the Japanese (19) and the Dutch (20) groups. Subjects included for study were 50- to 79-year-old residents of the Rotterdam and Kyoto regions, including surrounding suburban and rural areas. Foreign-born residents who did not have adequate command of the Dutch language were excluded from...
controls are shown by age group. The age groups were chosen to present Table 1 the total numbers of identified and included subjects with collected blood was then centrifuged, and the plasma and saliva samples were stored at -20°C until analysis. The Japanese samples were sent from the Japanese subjects. No saliva was collected from the cooperating Dutch subjects, while 20 ml of heparinized blood was collected from the Dutch study. Clinical cases were identified from new admissions for prostatic cancer and BPH. In addition, from the university hospitals and other participating hospitals, pathological specimens from transurethral resections and subcapsular prostaticctomies were reviewed following a protocol (21) to identify additional cases of focal prostatic cancer to implement the number of those found at the time of routine pathological examination. Control patients with a history of cancer, liver disease, or BPH were excluded from study. Each cooperating study subject was personally interviewed using a detailed questionnaire which included a demographic history, a history of marital status and sexual behavior, and a dietary history. In addition, 20 ml of heparinized blood and 5 ml of saliva were collected from cooperating Dutch subjects, while 20 ml of heparinized blood was collected from the Japanese subjects. No saliva was collected from the Japanese subjects because this item was added to the protocol after a number of blood samples had been collected from Japanese men, making it impossible to obtain a complete set of data. Biological samples were collected between 9 a.m. and 12 noon. Samples were kept cool until they could be further processed, usually within 1–2 h. The collected blood was then centrifuged, and the plasma and saliva samples were stored at −20°C until analysis. The Japanese samples were sent to Rotterdam on solid CO₂. Patients who had been treated by surgical or chemical castration (Rotterdam, n = 9; Kyoto, n = 17) were excluded from the study. In Table 1 the total numbers of identified and included subjects with clinical and focal prostatic cancer and with BPH and the number of controls are shown by age group. The age groups were chosen to present data for approximately equal numbers of Dutch patients in each group. The number of subjects for whom plasma hormone analyses were included in further calculations are also shown. Overall, about equal numbers of patients with clinical cancer and BPH and controls were identified for study, along with a smaller number of focal prostate cancer patients. Compared to the other three groups, an excess of carcinomma patients no stage-dependent difference in hormonal levels was detected; for this reason the data have been shown as data from one group of patients.

Hormone Estimations. All hormone estimations in the samples from the Dutch and Japanese men were performed in one laboratory. Assays of samples from Dutch and Japanese subjects were performed in random order, depending on the availability of samples in the laboratory at the time of assay. Plasma and saliva concentrations of testosterone were estimated by radioimmunooassay in non-chromatographed samples, using the method described earlier (22). Plasma concentrations of 5α-dihydrotestosterone were estimated using the same antisera, after separation of dihydrotestosterone from testosterone on silica gel microcolumns (23). SHBG was estimated by measuring binding of [3H]5α-dihydrotestosterone (24). Finally, the plasma concentration of estradiol was measured using kits provided by Clinical Assays (Cambridge, MA). Intra- and interassay variences, observed during the period in which the assays were performed and expressed as coefficients of variation, were <12 and <15%, respectively.

Statistical Methods. Hormonal values, obtained in the various subgroups in this study, showed no substantial deviation from the normal distribution after visual inspection of histograms and applying Kolmogorov-Smirnov tests to the results of the groups. For this reason, Pearson correlation coefficients were used to investigate the relationships between various parameters.

In order to compare hormone levels in different groups, analysis of covariance was carried out adjusting for age (25). Raw data (means ± SEM) and age-adjusted means are presented. In multiple comparisons, the Bonferroni correction was applied to the levels of significance.

For categorical analyses, the values of the hormone levels were divided into low, moderate, and high categories, based on the 25th and the 75th percentiles as found in the control group. Odds ratios, corrected for age, corresponding to moderate and high values and the respective trend tests (26) were calculated using the low category as a baseline.

RESULTS

Differences between Hormone Levels in Dutch and Japanese Men and Effects of Age and Body Weight. Results of the estimations of the hormones in the control groups of Dutch and Japanese men have been summarized in Table 2. The mean age of the Dutch men was significantly lower than that of the Japanese men. Since a number of the hormonal parameters was significantly correlated with age (Table 3), P values shown in Table 2 are for raw data and for concentrations after age correction. If this correction was not applied, the plasma concentrations of testosterone and estradiol were also significantly higher in the Dutch than in the Japanese men. The significance of the difference between SHBG levels, present if the age correction was not applied (P = 0.016), was lost after this correction. Age correction did not alter the significance of:

Table 2 Hormone levels in normal Dutch and Japanese men (means ± SEM)
P values for the significance of differences between hormone levels were calculated before age correction (Student’s t test) and on basis of age-corrected data (covariance analysis; after).

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Dutch (n = 123)</th>
<th>Japanese (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Plasma T (nmol/liter)</td>
<td>62.9 ± 0.6</td>
<td>69.8 ± 0.7</td>
</tr>
<tr>
<td>DHT (nmol/liter)</td>
<td>23.7 ± 0.09</td>
<td>23.8 ± 0.10</td>
</tr>
<tr>
<td>SHBG (nmol/liter)</td>
<td>59.8 ± 2.2</td>
<td>59.9 ± 0.9</td>
</tr>
<tr>
<td>Estradiol (pmol/liter)</td>
<td>81.8 ± 2.7</td>
<td>71.2 ± 3.8</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.43 ± 0.02</td>
<td>0.43 ± 0.03</td>
</tr>
<tr>
<td>DHT/T</td>
<td>0.099 ± 0.004</td>
<td>0.10 ± 0.004</td>
</tr>
</tbody>
</table>

* P < 0.05.
** P < 0.01.
*** P < 0.001.
differences in the ratios of testosterone to SHBG but caused a
mean difference in the ratio of dihydrotestosterone to
testosterone. Mean body weights in the various groups of pa-
tients and controls were not different (data not shown). In
the Dutch men, this parameter was not highly, but significantly,
correlated with plasma concentrations of testosterone (r =
-0.18, P < 0.001), and SHBG (r = -0.30, P < 0.001) and the ratio between
testosterone and SHBG (r = 0.12, P < 0.01). In the Japanese
men, only a significant correlation between body weight and
SHBG (r = -0.11, P < 0.05) was found.

Hormone Levels in Control, Benign Prostatic Hyperplasia,
and Prostatic Carcinoma Subjects. Results of hormone estima-
tions in the separate study groups are shown in Tables 4 and 5
for the Dutch and Japanese subjects, respectively. The age of
the men in the Dutch control group was significantly lower
than that in the other Dutch groups. Because of the relatively
small effect of age correction on the results (see Table 2), only
raw data are shown. The statistical significance of differences,
however, was calculated on the basis of age-corrected data.
Plasma hormone concentrations in the Dutch control group
were not significantly different from those in the Dutch pro-
static carcinoma, focal carcinoma, and benign prostatic hyper-
plasia groups. No significant differences in hormone levels in
the 3 patient groups could be detected either. Plasma hormone
levels in the prostate carcinoma group were not correlated
with the stage of the disease. Treatment involving the prostate
did not affect hormonal parameters either; e.g., dihydrotestosterone
levels in 38 prostatectomized or transurethral resection-treated
patients were 2.09 ± 0.19 (SEM) versus 2.14 ± 0.06 nmol/liter
in the nontreated group. Relative risk analysis for the parameters
estimated added extra information: the trend test yielded a
significant result (P < 0.05) for plasma testosterone in the
prostatic carcinoma group versus the control group. Relative
risk values were 0.81 (P = 0.63) and 0.40 (P = 0.05) for the
middle and high testosterone prostatic carcinoma groups, when
compared with the low testosterone group.

In the Japanese men, no significant differences were found
between the ages of subjects in the various groups (Table 5).
There were no differences between hormone levels in the control
group and the focal or clinical carcinoma group. However,
SHBG concentrations in the benign prostatic hyperplasia group
were significantly lower than those in the controls and in the
men with clinical prostatic carcinoma, while the ratios of tes-

tosterone to SHBG and of dihydrotestosterone to testosterone
were significantly larger in the benign prostatic hyperplasia
group when compared with controls. Relative risk analyses for
these parameters also indicated the significance of the differ-
ences shown in Table 2 for the control groups were also present
for the groups of benign prostatic hyperplasia patients and
clinical carcinoma patients. Finally, the difference between
Dutch and Japanese men with respect to the ratio of testoster-

Table 3 Pearson correlation coefficients for the relationships between age and
hormonal parameters in Japanese and Dutch men

<table>
<thead>
<tr>
<th>Hormonal parameter</th>
<th>Dutch (n = 368)</th>
<th>Japanese (n = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>-0.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Saliva</td>
<td>-0.12*</td>
<td></td>
</tr>
<tr>
<td>DHT</td>
<td>-0.06</td>
<td>-0.01</td>
</tr>
<tr>
<td>SHBG</td>
<td>0.29*</td>
<td>0.28*</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.20*</td>
<td>0.06*</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>-0.19*</td>
<td>-0.08</td>
</tr>
<tr>
<td>DHT/T</td>
<td>-0.06</td>
<td>-0.11*</td>
</tr>
</tbody>
</table>

* P < 0.001.
* P < 0.01.
* P < 0.05.

Table 4 Age and hormonal parameters in Dutch controls and men with benign prostatic hyperplasia, focal prostatic carcinoma, and prostatic carcinoma (means ± SEM)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Control (n = 123)</th>
<th>BPH (n = 119)</th>
<th>Focal (n = 36)</th>
<th>Prostatic carcinoma (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.9 ± 0.6</td>
<td>67.1 ± 0.6*</td>
<td>68.8 ± 0.9*</td>
<td>66.2 ± 0.8*</td>
</tr>
<tr>
<td></td>
<td>23.7 ± 0.9</td>
<td>21.5 ± 0.7</td>
<td>20.9 ± 1.1</td>
<td>20.9 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>0.23 ± 0.01</td>
<td>0.22 ± 0.01</td>
<td>0.22 ± 0.02</td>
<td>0.22 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>2.28 ± 0.10</td>
<td>2.11 ± 0.09</td>
<td>2.09 ± 0.15</td>
<td>2.15 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>59.8 ± 2.2</td>
<td>57.0 ± 1.9</td>
<td>60.4 ± 4.1</td>
<td>57.5 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>81.8 ± 2.7</td>
<td>82.0 ± 2.6</td>
<td>84.5 ± 5.0</td>
<td>83.6 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>0.43 ± 0.03</td>
<td>0.40 ± 0.01</td>
<td>0.39 ± 0.03</td>
<td>0.38 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>0.09 ± 0.004</td>
<td>0.103 ± 0.004</td>
<td>0.104 ± 0.007</td>
<td>0.104 ± 0.004</td>
</tr>
</tbody>
</table>

* Significantly different when compared with control group at the level of 0.05/3 = 0.016 (Bonferroni correction).

Table 5 Age and hormonal parameters in Japanese controls and men with benign prostatic hyperplasia, focal prostatic carcinoma, and prostate carcinoma (means ± SEM)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Control (n = 91)</th>
<th>BPH (n = 89)</th>
<th>Focal (n = 6)</th>
<th>Prostatic carcinoma (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.8 ± 0.7</td>
<td>69.8 ± 0.6</td>
<td>73.7 ± 1.2</td>
<td>70.5 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>20.3 ± 1.0</td>
<td>19.4 ± 1.0</td>
<td>23.3 ± 4.2</td>
<td>18.3 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>2.03 ± 0.10</td>
<td>2.41 ± 0.17</td>
<td>2.33 ± 0.45</td>
<td>2.12 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>69.2 ± 3.0</td>
<td>55.5 ± 2.4*</td>
<td>65.2 ± 7.6</td>
<td>66.1 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>71.2 ± 3.8</td>
<td>68.8 ± 4.1*</td>
<td>78.0 ± 14.1</td>
<td>67.4 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>0.32 ± 0.02</td>
<td>0.39 ± 0.02*</td>
<td>0.36 ± 0.05</td>
<td>0.35 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.106 ± 0.004</td>
<td>0.127 ± 0.006*</td>
<td>0.101 ± 0.015</td>
<td>0.121 ± 0.008</td>
</tr>
</tbody>
</table>

* Significantly different when compared with control group at the level of 0.05/3 = 0.016 (Bonferroni correction).
one to SHBG was only present in the control group and not in the prostatic carcinoma or benign prostatic hyperplasia patients.

Relationships between Hormone Levels. Pearson correlation coefficients and significances of correlations for the interrelationships between hormone levels have been summarized in Tables 6 and 7. The results for the 368 Dutch and the 258 Japanese men were usually very similar. The only exceptions in this respect were the relationships between DHT or estradiol levels and the ratio between testosterone and SHBG (which showed no correlation in the Dutch group, while the correlation coefficients were about 0.2 in the Japanese group) and between SHBG levels and the DHT/T ratio (which was not significant in the Japanese group, whereas it was significant in the Dutch group).

Similarly, when correlations were significant for the total groups of Dutch or Japanese men, significant correlations were also found in the various patient groups, with the general exception of the Japanese group with focal prostatic carcinoma, which contained only 6 patients.

DISCUSSION

One of the hypotheses, on which this part of the Dutch-Japanese case-control study of prostatic cancer was based, was that there might be differences between the hormone levels in populations of Dutch and Japanese men, because of the difference in incidence of prostatic carcinoma in the two countries. Interlaboratory differences between results for hormone levels in samples from the two countries were excluded by measuring all hormone concentrations in one laboratory. The results, summarized in Table 2, support the hypothesis: the concentrations of testosterone and estradiol were significantly higher in the Japanese controls, when compared to the results for the Japanese men who moved to Hawaii have been reported (16); in that study no American control group was included, however. Also, in that group of men the hormone levels, which were measured in samples taken before the carcinoma became apparent, were within the normal range for Western countries. A similar study in which hormones were measured in Nigerian and American blacks (low and high incidence of prostatic cancer, respectively) reported lower testosterone levels in the Nigerians when compared with the Americans (27). However, those data were contradicted in a later study (28). Finally, Ross et al. (29) described higher levels of total and free testosterone in young American blacks, when compared with young American white men. The authors indicate that the observed 15% difference might explain the 2-fold difference in prostatic cancer risk.

The higher testosterone levels in the plasma from the Dutch subjects, together with similar levels of SHBG and dihydrotestosterone in the two populations, caused a significantly higher testosterone to SHBG ratio and a significantly decreased dihydrotestosterone to testosterone ratio in the Dutch group. These observations might indicate that the non-protein-bound levels of testosterone are higher in the Dutch men, when compared to those in the Japanese. Estimation of salivary testosterone in the Japanese men would clarify this point further. It is difficult to extrapolate these peripheral hormone levels to the intraprostatic concentrations of the androgens, since most of the intraprostatic dihydrotestosterone is likely to be formed locally. The reason for the differences between dihydrotestosterone to testosterone ratios in the Dutch and Japanese population, which indicates different peripheral 5α-reductase activities in the two groups, remains unclear. As discussed, age and body weight do not affect the differences in a significant way. However, it is possible that dietary factors play a role in this respect (30, 31).

The absence of correlation between age and peripheral testosterone levels in both groups of men adds to the existing controversy about this subject. A large number of studies indicate a decrease of peripheral testosterone levels with age (10, 32–35), while other investigators (36–38) suggested that testosterone levels may decrease in inhabitants of homes for the aged or hospital patients but not in healthy, active elderly men. The increased level of SHBG in older men has been described by all of the above-mentioned authors; this increase of SHBG is likely to be the cause of the negative correlation of salivary testosterone levels with increasing age observed in this study. Since the salivary testosterone concentration is a reflection of the concentration of the non-protein-bound hormone in plasma (39), this observation indicates that levels of “biologically active” androgens decrease with increasing age, despite similar plasma concentrations of total androgens in younger and older men.

The age differences between the various groups of Dutch participants in this study necessitated the use of age correction of the hormone levels before comparison of the data in the different groups; these corrections had only very limited effect in the interpretation of results. Plasma testosterone concentrations in the groups with benign prostatic hyperplasia, focal prostatic carcinoma, and clinically evident prostatic carcinoma were not significantly different from those in the control group. Similarly, the other parameters studied showed no differences between the various groups (Table 4), indicating that the amount of circulating free androgens, as reflected by the salivary concentration of testosterone or the testosterone to SHBG ratio, was not different between the controls and the three patient groups. The ratio between dihydrotestosterone and tes-

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Table 6 Pearson correlation coefficients for the interrelationship between hormone levels in the 368 Dutch men

<table>
<thead>
<tr>
<th>Plasma T</th>
<th>Salivary T</th>
<th>DHT</th>
<th>SHBG</th>
<th>Estradiol</th>
<th>T/SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary T</td>
<td>0.24*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHT</td>
<td>0.53*</td>
<td>0.14*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>0.52*</td>
<td>-0.01</td>
<td>0.50*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.24*</td>
<td>0.18*</td>
<td>0.19*</td>
<td>0.19*</td>
<td></td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.42*</td>
<td>0.29*</td>
<td>0.02</td>
<td>-0.48*</td>
<td>0.03</td>
</tr>
<tr>
<td>DHT/T</td>
<td>-0.22*</td>
<td>-0.09</td>
<td>0.65*</td>
<td>0.10*</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* p < 0.001.
# p < 0.01.
% p < 0.05.

Table 7 Pearson correlation coefficients for the interrelationship between hormone levels in the 258 Japanese men

<table>
<thead>
<tr>
<th>Plasma T</th>
<th>DHT</th>
<th>SHBG</th>
<th>Estradiol</th>
<th>T/SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHT</td>
<td>0.58*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>0.42*</td>
<td>0.33*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.48*</td>
<td>0.45*</td>
<td>0.22*</td>
<td></td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.41*</td>
<td>0.18*</td>
<td>-0.46*</td>
<td>0.18*</td>
</tr>
<tr>
<td>DHT/T</td>
<td>-0.17*</td>
<td>0.62*</td>
<td>0.05</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* p < 0.001.
# p < 0.01.
testosterone levels was not significantly changed in the patients with prostatic pathology either.

In the Japanese group, the only striking observation was a reduced plasma SHBG level in the benign prostatic hyperplasia group, when compared with the level in the control group. The reason for this difference is not clear and is unlikely to be due to a storage or shipping problem, because the other subgroups were unaffected. This decreased SHBG concentration is most likely to be the cause of the increased testosterone to SHBG ratio in this group. It is not clear, however, why in this group the ratio between dihydrotestosterone and testosterone is also increased, when compared to the controls: decreased binding of testosterone might favor its conversion to dihydrotestosterone, on the one hand, but decreased metabolism of the androgens, on the other hand.

Comparison of the data obtained in this study with earlier reported plasma hormone concentrations in men with prostatic disease, as earlier summarized by Flanders (40), leads to the conclusion that reported significant differences between androgen levels in controls and patients with benign prostatic hyperplasia or prostatic carcinoma are probably unrelated to the cause of the prostate disease. From the present results it becomes clear that differences in age of the study groups or secondary effects of the disease are not likely explanations for these differences: age correction did not affect the results and hormone levels were not related to stage of prostatic cancer, as reported earlier (41). However, disease-related stress may suppress testosterone levels as was recently reported for lung cancer patients (42). The observation of similar free testosterone levels, estimated as salivary testosterone concentrations, in all Dutch groups in this study stresses this point. The absence of common changes in hormone levels in the Dutch and Japanese participants in this study do not support the presence of generally applicable principles in the relationship between the occurrence of prostatic cancer and peripheral hormone levels. However, time of studying plasma levels may be of crucial importance. Early events in the pathogenesis of clinical prostate cancer, i.e., the promotion from focal to clinical disease, may still be related to differences in endocrine parameters.

The relationships between the hormonal parameters shown in Tables 6 and 7 confirm a number of physiological observations, reported for smaller groups of male subjects, and indicate the validity of the hormonal measurements. The role of testosterone as a precursor of both dihydrotestosterone and estradiol is indicated by the high correlations between plasma levels of products and precursor. The relationship between salivary concentrations of testosterone and the plasma testosterone to SHBG ratio is higher than that between salivary and plasma testosterone. This indicates that the salivary level of testosterone can be a better reflection of “free testosterone” concentration in plasma than total testosterone. The positive correlation between plasma testosterone levels and SHBG indicates that it is, rather, the negative effect of SHBG on testosterone metabolism (43) than the negative effect of testosterone on SHBG biosynthesis, which dictates the relationship between the concentrations of these two substances. In those instances, in which different regression lines were found for the Dutch and Japanese men, SHBG and estradiol were involved. Both SHBG (44) and estradiol levels in peripheral plasma are related to body mass; this factor might play a role in causing these differences, since the Dutch men were generally heavier than the Japanese subjects.

In summary, this study confirmed the results of a number of publications on hormone levels in elderly men. This indicates the validity of the assay systems used. Nevertheless, no consistent changes in hormone levels, which accompanied the presence of benign prostatic hyperplasia or prostatic cancer, were found in the large groups of subjects investigated. These findings do not support the hypothesis that hormonal parameters play a primary role in the origin or outgrowth of prostatic abnormalities.

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