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Pretreatment Plasma Testosterone and Estradiol Levels in Patients With Locally Advanced or Metastasized Prostatic Cancer

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BACKGROUND. Studies concerning pretreatment plasma hormonal environment in relation to stage of prostatic cancer have given conflicting results. The aim of the present study was to compare the pretreatment plasma testosterone (T), free T (fT), estradiol (E2), and free E2 (fE2) levels in patients with locally advanced (T3–4 M0) and metastatic (T1–4 M1) prostatic cancer, and to further examine the effect of the patients' general condition on these levels.

METHODS. The present series consisted of 238 patients (Finnprostate 6 study). The variables analyzed were E2, fE2, T, fT, age, body mass index (BMI), sex hormone binding globulin capacity (SHBG), prostate-specific antigen (PSA), alkaline phosphatase (ALP), hemoglobin concentration (Hb), erythrocyte sedimentation rate (ESR), and performance status (PS).

RESULTS. The E2 and fE2 levels were significantly higher in M0 patients than in M1 patients, with no significant differences in T and fT levels. In multivariate analyses, a decline in performance status (PS), an increase in ESR, or a decrease in Hb, were related to a decrease in T, fT, E2, or fE2 levels.

CONCLUSIONS. Pretreatment plasma estradiol was significantly lower in M1 patients than in M0 patients, but there were no significant differences in T levels, although the poor general condition was related to a decrease in the pretreatment levels of both testosterone and estradiol. *Prostate 39:175–181, 1999.*

KEY WORDS: **sex steroid hormones; general condition; performance status; hemoglobin concentration; erythrocyte sedimentation rate; body mass index**

INTRODUCTION

The normal physiology of the human prostate is dependent on both androgens and estrogens [1,2]. To improve the understanding of the etiology of prostatic cancer, several studies have been conducted to compare the pretreatment plasma hormone levels in prostatic cancer patients with the hormone levels in healthy controls. In a review of case-control studies, the results concerning testosterone (T) and estradiol (E2) levels were controversial [3]. Also, studies concerning pretreatment plasma hormonal environment in relation to stage of prostatic cancer have given conflicting results [3–5]. In earlier studies, the E2 and estrone (E1) levels were lower in M1 patients than in M0 patients, and even the T level was lower in M1 patients than in M0 patients [6,7]. It has been suggested that the difference in these hormone levels between metastatic and nonmetastatic disease probably simply reflect the more stressful and catabolic condition and poorer general condition of patients with disseminated malignant disease [7]. On the other hand, we previously found that pretreatment plasma E2 and free estradiol (fE2) levels were significantly lower in M1 patients than in M0 patients [8], with no significant differences in total T and free testosterone (fT) levels

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[9]. The ratio of T to sex hormone binding globulin capacity (SHBG) was significantly higher in M0 patients than in M1 patients [9]. Moreover, in a recent study, the pretreatment E1 level was lower in M1 patients than in M0 patients, with no significant differences in T levels [10]. These findings raise the question of whether the difference in estrogen levels between M0 and M1 patients is merely a result of the poorer general condition of M1 patients. We previously suggested that high endogenous E2 levels may inhibit the growth and metastasizing tendency of prostatic cancer [8]. Aging [11,12] and obesity [13–15] are factors that increase the E2/T ratio. In our previous studies of testosterone and estradiol levels, there were no significant differences in the age distribution and mean BMI between M1 and M0 patients [8,9].

Prostatic cancer studies commonly use a five-point performance status scale, either of the Eastern Cooperative Oncology Group or of the World Health Organization (WHO), in the evaluation of general condition [16,17]. Additional information about general condition may be obtained by the use of hemoglobin concentration (Hb) and erythrocyte sedimentation rate (ESR). Several chronic and malignant diseases are associated with an increase in ESR and/or a decrease in Hb [18].

The aim of the present study was to compare the pretreatment plasma T, fT, E2, and fE2 levels in patients with locally advanced (T3–4 M0) and metastasized (T1–4 M1) prostatic cancer, and to further examine the effect of the patients' general condition on these levels.

MATERIALS AND METHODS

The present series consisted of 238 patients between age 45–91 years (mean, 73 years) with histologically and/or cytologically verified prostatic cancer diagnosed between January 1990–March 1994 in a Finnish multicenter prostatic cancer study, Finnprostate 6. Histologic and/or cytologic grading was done according to the WHO classification [19], and the TNM system was used for staging of the disease [20]. Only patients with T3–4 M0 or T1–4 M1 prostatic cancer were included in the study. Exclusion criteria were patient refusal, noncompliance, other malignancy except skin cancer (not melanoma), previous hormone therapy, symptomatic coronary heart disease, or contraindications to estrogen therapy (untreated heart failure, previous pulmonary embolism or deep vein thrombosis, permanent antithrombotic therapy, hepatic failure). Of the 458 patients included in the Finnprostate 6 study, 2 were excluded because of protocol violation and 218 because of missing data for at least one variable used in the present study.

TABLE I. Number and Percentage of Patients According to TM and G Classifications

	G1		G2		G3		Total
	n	%	n	%	n	%	(n)
T3–4 M0	37	(28.9)	72	(56.3)	19	(14.8)	128
T1–4 M1	24	(21.8)	65	(59.1)	21	(19.1)	110
Total	61	(25.6)	137	(57.6)	40	(16.8)	238

Measurement of plasma T, E2, and SHBG levels was performed as described previously [21–23]. fT was calculated using the formula $fT = T \times 0.01 \times (3.66 - 1.38 \times \log_{10} SHBG\ (nmol/l))$ [24]. The measured and calculated values correlated relatively well (r = 0.80). fE2 was calculated using the formula $fE2 = E2 \times 0.01 \times \exp(0.389 - 0.003 \times SHBG\ (nmol/l))$ [25]. We previously checked the validity of this calculation, and the calculation method gave slightly lower values for free E2 (20%) than the direct assay [8]. Performance status was graded as follows: 0, no symptoms; 1, symptoms but ambulatory; 2 = ≤50% bedridden; 3, >50% bedridden; and 4 = 100% bedridden (WHO grading system).

Age, body mass index (BMI) [26], prostate-specific antigen (PSA), alkaline phosphatase (ALP), ESR, Hb, and performance status (PS) were used to explain individual variation in T and fT. In addition, T and fT were used to explain the individual variation in E2 and fE2. PS, ESR, and Hb were used to reflect the general condition of patients. PSA and ALP were included in this study model because, to a certain degree, PSA is associated with stage of prostatic cancer [27] and ALP with extent of bone involvement [28].

The results are given as arithmetic means and 95% confidence intervals (CI). Student's *t*-test was applied to compare the means in the M0 and M1 groups. The logarithmic (ln) transformation was used for PSA, ALP, and ESR in all analyses (lnPSA, lnALP, and lnESR, respectively) because of the nonlinear nature of these variables. The hormone levels were described with linear regression; the best subset regression was used. Mallow's C_p was used to determine the best subset. All statistical analyses were made using the BMDP program.

RESULTS

The distribution of patients according to TM and G classifications is presented in Table I. There were 128 patients in the M0 group and 110 in the M1 group, with a slight tendency to a higher grade in M1 patients, but the difference was not statistically significant ($\chi^2 = 1.8$).

TABLE II. Arithmetic Mean and 95% CI of Pretreatment Variables According to Stage (T3–4M0 or T1–4M1)*

		M0 (n = 128)	M1 (n = 110)	M0 vs. M1 (*t*-test)
Age	mean	73.6	72.7	$P = 0.34$
years	95% CI	72.5–74.7	71.2–74.2	
BMI	mean	26	24.4	$P < 0.01$
kg/m^2	95% CI	25.4–26.6	23.7–25.1	
E2	mean	87.9	74.7	$P < 0.01$
pmol/l	95% CI	81.9–93.9	69.2–80.2	
fE2	mean	1.13	0.95	$P < 0.001$
pmol/l	95% CI	1.05–1.21	0.88–1.02	
T	mean	16.4	15.7	$P = 0.42$
nmol/l	95% CI	15.2–17.6	14.4–17.0	
fT	mean	0.22	0.21	$P = 0.14$
nmol/l	95% CI	0.21–0.23	0.19–0.23	
SHBG	mean	46.2	50.5	$P = 0.12$
nmol/l	95% CI	42.9–49.5	46.2–54.8	
PSA	mean	52	557	$P < 0.001$
mg/l	95% CI	36–68	297–817	
	g-mean	29	152	$P < 0.001$
	95% CI	25–35	112–205	
ALP	mean	186	468	$P < 0.001$
U/l	95% CI	160–212	317–619	
	g-mean	167	280	$P < 0.001$
	95% CI	156–180	239–328	
Hb	mean	141	134	$P < 0.01$
g/l	95% CI	138–144	131–137	
ESR	mean	16	29	$P < 0.001$
mm/hr	95% CI	13–19	24–34	
	g-mean	11	18	$P < 0.001$
	95% CI	9.0–13.0	14–22	
PS	mean	0.31	0.78	$P < 0.001$
	95% CI	0.21–0.41	0.62–0.94	

*g-mean, geometric mean.

The means and 95% CI of the pretreatment variables according to M classification (M0 or M1) are presented in Table II. There was no significant difference in age distribution between groups, but BMI was significantly lower in M1 patients. In M0 patients, E2 and fE2 levels were significantly higher than in M1 patients (87.9 pmol/l and 1.13 pmol/l, and 74.7 pmol/l and 0.95 pmol/l, respectively), whereas T and fT levels were almost similar (16.4 nmol/l and 0.22 nmol/l, and 15.7 nmol/l and 0.21 nmol/l, respectively). As expected, the ESR, PSA, and ALP levels were significantly higher and the Hb level significantly lower in M1 patients. Likewise, PS was significantly poorer in M1 patients. It was reduced in 33 (26%) M0 patients and in 63 (57%) M1 patients. In M0 patients, PS was 1 in 27 and 2 in 6 cases, and in M1 patients it was 1 in 47 cases, 2 in 10 cases, 3 in 5 cases, and 4 in one case. There were no significant differences in the ratios of T/SHBG, T/E2, T/fE2, fT/E2, and fT/fE2 (data not shown).

When M0 and M1 patients were divided into groups according to differentiation grade (G1–G3) of carcinoma, there were no significant differences in pretreatment hormone levels, their ratios, and other variables between G1, G2, and G3 categories.

The multivariate technique that allows all variables to act together was used to find out the most significant groups of variables, which explained the individual variation in T, fT, E2, and fE2. M0 and M1 patients were analyzed separately.

The regression coefficients of variables which gave the best explanation of the individual variation in T and fT in M0 and M1 patients are presented in order of importance in Table III. In M0 patients, an increase in BMI and a decrease in Hb were related to the decrease in T level. An increase in BMI and age, and a decrease in Hb, were related to a decrease in fT level. In M1 patients, an increase in BMI, PS scale, and ESR, and a decrease in age, were related to a decrease in T level. An increase in BMI and PS scale, and a decrease in Hb, were related to a decrease in fT level.

The regression coefficients of variables which best explained individual variation in E2 and fE2 in M0 and M1 patients are presented in order of importance in Table IV. In M0 patients, a decrease in T and Hb, and an increase in ESR, were related to a decrease in E2 level. A decrease in T, BMI, and Hb, and an icrease in ESR, were related to a decrease in fE2 level. In M1 patients, a decrease in fT, BMI, Hb, and age were related to a decrease in both E2 and fE2 levels.

DISCUSSION

In this study, the estradiol level was significantly lower in prostatic cancer patients with, as opposed to without, metastases. The major portion of plasma estradiol is derived from peripheral conversion of testosterone, produced mainly by the testes; in normal men, 25% or less of plasma estradiol is derived by direct secretion from the testes and only small amounts from the adrenal glands [29,30]. This is in accordance with our finding that testosterone explained most of the individual variation in estradiol. However, there was no significant difference in testosterone levels between patients with and without metastases. Earlier reports indicated that an increase in the E2/T ratio in healthy men correlates with obesity [13–15] and aging [11,12]. This association was seen also in our study. In fact, BMI explained most of the

TABLE III. Regression Equations and 95% CI for T and fT With the Best Models (Mallow's C_p) for M0 and M1 Patients*

M0					
T			fT		
Variable	b	95% CI	Variable	b	95% CI
Intercept	23.5	10–37	Intercept	0.37	0.13–0.61
BMI	−0.65	−0.97–−0.33	BMI	−0.0045	−0.0081–−0.0009
Hb	0.069	−0.012–0.15	Hb	0.001	0.0001–0.0019
			Age	−0.0022	−0.0043–−0.0001
$P < 0.001$			$P < 0.01$		
M1					
T			fT		
Variable	b	95% CI	Variable	b	95% CI
Intercept	20.2	6.0–34.4	Intercept	0.19	0.05–0.33
BMI	−0.39	−0.71–−0.07	BMI	−0.004	−0.007–−0.001
PS	−3.11	−4.61–−1.61	PS	−0.03	−0.05–−0.01
InESR	−1.06	−2.26–0.14	Hb	0.001	0.0001–0.0019
Age	0.14	−0.01–0.29			
$P < 0.001$			$P < 0.001$		

*Variables are listed in order of importance. b, regression coefficient.

individual variation in T and fT in M0 and M1 patients, and the effect was inverse. It has been suggested that this inverse relationship between BMI and serum testosterone is mediated by the fat-derived protein, leptin [31], identified a few years ago, because of the following findings: 1) leptin highly correlates with BMI; 2) T and fT are highly inversely correlated with BMI; and 3) leptin also inversely correlates with T and fT values [32]. On the other hand, it has been found that the increase in testosterone level induces a decrease in serum leptin level [33–35]. BMI explained the second best individual variation in E2 and fE2 in M1 patients and fE2 in M0 patients. Age correlated positively with E2, fE2, and T variation in M1 patients and inversely with fT variation in M0 patients. These results prove clearly that BMI and age should always be considered in studies concerning sex steroid hormone levels in different patient groups.

Performance status is often used in prostatic cancer studies to evaluate patients' general condition [16,17,36,37]. However, this is a subjective method, and in borderline cases the classification of performance status may be quite random. In our study, performance status was classified as not reduced in 74% of M0 patients and in 43% of M1 patients, although it is unlikely that all these patients presented with the same general condition. ESR and Hb provide additional information in the evaluation of general condition. In prostatic cancer patients, an increase in ESR has been shown to correlate significantly with disease stage, fever, pain, elevation of white blood cell count, and decrease in Hb (r = -0.617) [38]. Also, in the present study there was a significant inverse correlation between ESR and Hb (r = -0.500) both in M0 and M1 patients (data not shown).

In our study model, performance status, ESR, and Hb reflected the general health status of patients. In M1 patients, performance status was second best at explaining the individual variation in testosterone, and the effect was inverse, i.e., a poorer performance status was related to a decrease in testosterone level. In addition, increased ESR was associated with a decrease in T, and decreased Hb with a decrease in fT. Performance status did not explain the individual variation in estradiol levels. The effect may have been mediated already by the change in testosterone levels. In addition, Hb was positively related to estradiol levels. Most M0 patients were in good general condition and, consequently, performance status had no statistically significant effect on sex hormone levels. Hb correlated positively with testosterone levels. Both increased ESR and decreased Hb were associated with a decrease in estradiol levels. These results prove the usefulness of ESR and Hb in addition to performance status in the evaluation of the effect of general health status on sex steroid hormone levels.

TABLE IV. Regression Equations and 95% CI for E2 and fE2 With the Best Models (Mallow's C_p) for M0 and M1 Patients*

M0					
E2			fE2		
Variable	b	95% CI	Variable	b	95% CI
Intercept	23.2	−43.2–89.6	Intercept	−0.45	−1.47–0.57
T	1.78	1.00–2.56	T	0.02	0.01–0.03
Hb	0.35	−0.06–0.76	BMI	0.015	−0.005–0.035
InESR	−5.73	−12.40–0.94	Hb	0.0045	−0.0007–0.0097
			InESR	−0.076	−0.162–0.01
$P < 0.001$			$P < 0.001$		
M1					
E2			fE2		
Variable	b	95% CI	Variable	b	95% CI
Intercept	−104	−167–−41	Intercept	−1.33	−2.12–−0.54
fT	170.7	108–233	fT	2.1	1.3–5.1
BMI	1.83	0.60–3.06	BMI	0.025	0.009–0.041
Hb	0.22	−0.07–0.51	Hb	0.0035	0.0002–0.0072
Age	0.94	0.37–1.49	Age	0.01	0.003–0.017
$P < 0.001$			$P < 0.001$		

*Variables are listed in order of importance. b, regression coefficient.

In the present study, poor general condition was associated with decreased testosterone and estradiol levels. However, we did not find any significant differences in testosterone levels between patients with and without metastases. BMI was significantly lower in patients with metastases, and the decrease in BMI was highly associated with an increase in testosterone levels and so, to a certain degree, this could have leveled off the difference in testosterone levels between patients with and without metastases. On the other hand, the lower BMI in patients with metastases correlated less with the decrease in estradiol level, and so did not explain the difference in estradiol levels. This speaks in favor of poorer general condition explaining at least partly the significantly lower estradiol level in patients with metastases.

The controversial results of studies comparing plasma hormone levels in prostatic cancer patients before treatment and healthy controls [3] may in fact be partly due to the effect of general condition of prostatic cancer patients. The mean plasma testosterone and estradiol levels measured several years before prostatic cancer was diagnosed have not been found to differ significantly between prostatic cancer patients and healthy controls [39–42], but high levels of testosterone, low levels of SHBG and estradiol [42], and high levels of androstenedione [40] have been associated with an increased risk of prostatic cancer. On the contrary, in a recent study, serum levels of testosterone and its metabolites were not associated with an increased risk of prostatic cancer [43].

The association of estrogens and prostatic cancer and benign prostatic hyperplasia has been studied extensively, but there is no conclusive evidence of a role of estrogens in prostatic diseases. We observed earlier that plasma E2 concentration and urinary estrogen excretion were significantly higher in patients with benign prostatic hyperplasia than in prostatic cancer patients, and we suggested that elderly men with low estrogen levels are at a higher risk of developing prostatic carcinoma [44,45]. Also, this difference in estrogen levels may be partly explained by the poorer general condition of prostatic cancer patients. In a previous study, it was suggested that the growth, local invasion, and metastasizing of prostatic cancer are inhibited by factors associated with obesity [46] such as increased endogenous estrogen and decreased testosterone [13–15].

It has been observed that the growth of androgen-responsive LNCaP human prostate cancer cell lines was significantly stimulated by physiological concentrations of estradiol [47]. Inversely, physiological concentrations of estradiol have been found to inhibit the growth of androgen-nonresponsive PC3 human pros-

tate cancer cell lines, and the inhibitory effect increased with increasing concentrations of estradiol [48]. Thus, it may be possible that the amount of androgen-responsive tumor cells is higher in prostatic cancer patients with high levels of estradiol, and therefore even endocrine therapy might be more efficient than in patients with low levels of estradiol.

In Japan and some other Asian countries, mortality from prostatic cancer is low despite the same incidence of latent and small or noninfiltrative prostatic carcinomas as in the Western countries [49]. It has been hypothesized that the diet in these countries, rich in phytoestrogens, is responsible for this difference [50]. Phytoestrogens, i.e., isoflavonoids and lignans, undergo metabolic conversions in the gut, resulting in the formation of hormone-like compounds with weak estrogen activity and with an ability to bind with low affinity to estrogen receptors [51–53]. These results support the view that estrogens may have an inhibitory effect on the progression of prostatic cancer. On the other hand, it has been suggested that the great ethnic differences in the risk of developing prostatic cancer may be mainly due to ethnic variation in genetically determined endogenous characteristics [54].

CONCLUSIONS

In summary, poor general condition was associated with a decrease in the pretreatment levels of both testosterone and estradiol. In the evaluation of general condition, the use of erythrocyte sedimentation rate and hemoglobin concentration in addition to performance status proved very useful. Pretreatment plasma estradiol levels were significantly lower in patients with metastatic prostatic cancer than in patients without metastases, but there were no significant differences in testosterone levels. BMI was lower in patients with metastases, and a lower BMI was highly associated with an increase in testosterone level and so, to a certain degree, this could diminish the difference in testosterone levels between patients with and without metastases. The lower BMI in patients with metastases was less associated with the decrease in estradiol level and so did not explain the difference in estradiol levels. We suggest that lower pretreatment estrogen levels are at least partly explained by poorer general condition of the patients with metastases. In addition, we suggest that high endogenous estrogen levels may have an inhibitory effect on the progression of prostatic cancer.

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