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Androgen receptors, serum androgen levels and survival of breast cancer patients

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Summary. Steroid receptor levels and serum androgen levels were determined in 61 breast cancer patients and 34 patients with non-malignant breast lesions. Testosterone and dehydroepiandrosterone-sulfate did not and androstenedione did show a difference between the two groups. Androgen levels had no influence on survival rates. Androgen receptor (AR) levels correlated with progesterone receptor levels, but not with estrogen receptor levels or with tumor stage. Patients with positive AR findings had a better survival rate; this was independent of tumor stage. AR findings may therefore be a prognostic index in breast cancer patients.

Key words: Breast cancer – Androgen levels – Steroid receptors – Androgen receptors – Survival

Introduction

Hormone receptors are widely used as indicators of prognosis for breast cancer and as criteria for adjuvant therapy [5, 14, 16]. Originally, attention focussed on estrogen receptor levels. However, recent publications disclosed the predictive value of both progesterone receptor (PgR) levels [27] and of androgen receptors (AR) [6]. It was suggested that androgen receptors add information regarding both survival and response to endocrine treatment [18, 25].

There are controversial reports in literature about the importance of androgens in the growth and spread of breast cancer. A subnormal production of androgens was assumed to be a genetic marker of a disposition to breast cancer [26]. Elevated testosterone levels have been observed in premenopausal breast cancer patients [15], elevated testosterone and androstenedione levels in women with breast cancer or ductal hyperplasia as compared to controls [24]. This result

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has not been confirmed by others [13]. The conversion of androstenedione to estrone by breast cancer tissue was thought to have significance in promoting tumor growth [2].

We therefore studied the associations between serum androgen levels in breast cancer and fibroadenoma patients. In a second part of the study, the effect of serum androgen levels and androgen receptors on the survival of breast cancer patients was determined.

Materials and methods

We studied a consecutive series of 61 women (15 premenopausal, 46 postmenopausal) with stage I–III breast cancer; 34 women with benign breast disease who were matched for age and menopausal status (9 premenopausal, 25 postmenopausal), served as controls (patient data see Table 1). All patients were treated at the Ist Department of Obstetrics and Gynecology, Vienna, between September 1984 and June 1985. Surgery for cancer was a modified radical mastectomy with axillary dissection (Patey's procedure). Patients with positive axillary lymph nodes were given chemotherapy (6 courses of CMF [3]); subjects with positive estrogen receptors received tamoxifen. Distant metastases were excluded by radiology, ultrasonography, radio-isotope scan and biochemical tumor markers. Patients with benign lesions had a biopsy excision.

Table 1. Patient data

	Breast cancer (n = 61)	Benign breast lesions (n = 34)	
Age	n (%)	n (%)	
<40	4 (4.9)	3 (8.8)	
41–50 Pre-menopausal	13 (21.3)	6 (7.6)	
51–60	21 (34.4)	13 (38.2)	
61–70 Post-menopausal	18 (29.5)	11 (32.3)	
71–75	6 (9.8)	1 (2.9)	
Histology			
Ductal	47 (77.0)	Fibroadenoma:	25 (72.5)
Lobular	11 (18.0)	Fibrocyst.	
Mixed	3 (4.9)	Mastop.:	5 (14.5)
		Nodul. mastop.:	4 (11.6)
Tumor stage			
pT1	19 (31.3)		
pT2	29 (47.5)		
pT3	13 (21.3)		
Lymph nodes			
Positive	33 (54.1)		
Negative	28 (45.9)		
Hormone receptors			
ER+ (10 fmol/mg)	28 (45.9)		
PGR+ (10 fmol/mg)	25 (40.9)		
AR+ (10 fmol/mg)	24 (39.3)		

Three days before surgery, three blood samples were drawn between 8–10 a.m. at 20 min intervals from all patients and mean values were obtained to correct short time effects. All premenopausal subjects were in the follicular phase of the cycle. Serum levels of testosterone (T) were determined by radioimmunoassay using materials from Sorin (Sorin, Saluggia, Italy). This method utilizes a precipitating reagent for the separation of bound and free hormone. The determination of serum levels of androstenedione (A) was performed by a coated tube assay with materials provided by Diagnostic Products Cooperation (DPC, Los Angeles, CA). Prior to the radioimmunoassay an extraction with ether was performed. The estimation of dehydroepiandrosterone-sulfate (DHEA-S) serum levels was done with a coated tube solid phase radioimmunoassay by materials obtained from DPC. The inter- and intraassay coefficients of variation for the determination of serum androgen levels were 7 to 12%, respectively.

Tumor tissue samples from breast cancer patients were deep frozen in liquid nitrogen within 30 minutes of surgery. Estrogen (ER) and progesteron (PgR) receptor levels were determined by a double ligand DCC method described previously [10]. Similarily, the number of androgen receptor (AR) sites was determined by a DCC method which was reported recently, using ligand R 1881 [11]. AR receptor assays were done in the presence of a large excess of triamcinolone acetonide to account for interference with binding to progestin and glucocorticoid receptors. Evaluation of data was performed with Scatchard plot analysis [23]. Cut-off levels of the two assay systems were 10 fmol/mg protein. Intraassay coefficients of variation were 24% and 15% for ER and PgR, respectively. The interassay coefficients of variation were 13% and 23% for ER and PgR respectively.

Statistical analysis was supported by BMDP computer programs [9]. By means of a COX model [7] we determined, whether rank transformed [8] T, A, DHEA-S and AR values yielded prognostic information in addition to tumor stage. The reported p-values thus refer to a test of monotonic association of T, A, DHEA-S and AR with survival, adjusting for tumor stage. Differences in T, A, DHEA-S values between carcinoma and fibroadenoma patients are described by quantiles and evaluated by Wilcoxon's test. Monotonic associations of continous variables are described by Kendall's tau and corresponding error probabilities.

Results

T and DHEA-S serum levels (Table 2) did not differ significantly between the carcinoma and the fibroadenoma groups, whereas A was significantly higher for benign than for malignant conditions.

The distribution of receptor findings is shown in Table 3. 44 patients (72.1%) had at least one positive receptor finding, 17 (27.8%) were completely negative. 24 (39,3%) patients were AR+, 37 (60.6%) were AR−.

Table 2. Serum androgen levels and breast lesions ($n = 95$) (mean ± SD)

	Carcinoma ($n = 61$)	Fibroadenoma ($n = 34$)	P^a
T (ng/ml)	0.37 ± 0.23	0.28 ± 0.16	n.s.
A (ng/ml)	1.12 ± 0.49	1.43 ± 0.70	0.03
DHEA-S (ng/ml)	1.81 ± 1.55	2.13 ± 1.24	n.s.

a Wilcoxon 2-Sample test

Table 3. Distribution of estrogen receptor (ER), progesterone receptor (PgR) and androgen receptor (AR) status in breast cancer patients ($n = 61$)

	AR+	AR–	Σ
ER+/PgR+	8	4	12
ER+/PgR–	7	9	16
ER–/PgR+	6	7	13
ER–/PgR–	3	17	20
	24	37	61

Table 4. Kendall tau B correlation coefficients between androgens and steroid receptors ($n = 61$)

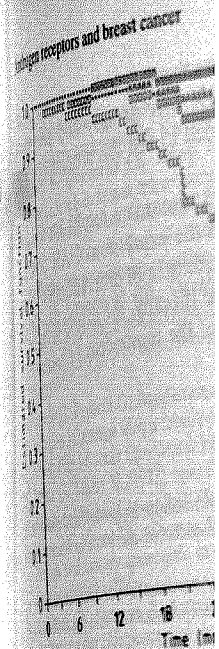|	T	A	DHEA-S	ER	PgR	AR
T	–					
A	0.220[a]	–				
DHEA-S	0.082	0.192[b]	–			
ER	0.025	– 0.029	– 0.021	–		
PgR	0.084	0.110	– 0.104	0.316[a]	–	
AR	0.138	0.344[b]	0.084	0.017	0.309[a]	–

[a] $P < 0.05$; [b] $P < 0.01$

Correlations between steroid receptors (Table 4) were present for ER and PgR and for PgR and AR. ER and AR did not show an association. AR did not show an association with tumor stage (chi2 = 0.7, n.s.).

Serum levels of T and DHEA-S (Table 4) did not show any association with steroid receptors, whereas A showed a highly positive correlation for AR, but none for ER and PgR. Menopausal status did not influence T and A levels; DHEA-S was higher for premenopausal cancer patients as compared to post-menopausal women (2.51 ± 1.54 vs. 1.67 ± 1.09, t-test n.s.).

22 patients (36%) had discordant results for ER and AR: 13 patients showed an ER+/AR– pattern, as compared to 9 patients with ER–/AR+. Discordant results between AR and PgR were present in 21 cases (34.4%): 11 times PgR+/AR–, 10 times PgR–/AR+. Survival rates between these 4 groups did not show a significant difference.

The mean overall observation time was 48 ± 3,4 months. As expected, tumor stage correlated highly with survival rates ($P = 0.003$). No influence of androgen levels on survival could be observed. Inclusion of lymph node status in the Cox model did not yield better discrimination. Androgen receptors showed a time-dependent association with survival rates, determined by the Cox model: patients with positive AR findings showed better overall survival rates irrespective of tumor stage (Fig. 1). At 48 months, the effect was less pronounced ($P = 0.1$) than at 36 months ($P = 0.08$). However, even at 48 months, relative risk (RR) as derived by the Cox model, remained 3 times higher for AR– patients as compared to AR+ patients (RR for tumor stage III vs. stages I/II: 14.2; RR for PgR– vs. PgR+: 1.5).
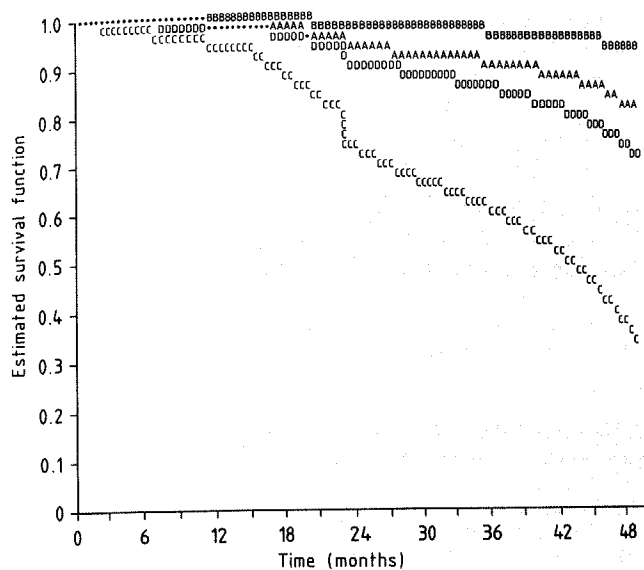
Fig. 1. Overall survival of 61 breast cancer patients, according to tumor stage and androgen receptor status. A = $T_{1,2}$/AR− (n = 28); B = $T_{1,2}$/AR+ (n = 20); C = T_3/AR− (n = 9); D = T_3/AR+ (n = 4)

Discussion

Our data suggest, that androgen levels in breast cancer patients are similar to those in patients with benign lesions. The lack of significant differences for T and DHEA-S levels confirms previous findings [13]. Differences between serum levels and urinary excretion might be the reason for contrasting results [22, 24]. Subnormal production of A had been observed previously [26]. Serum androgen levels did not prove to be of prognostic value for survival. The lack of significant correlations between T, DHEA-S serum levelse and AR findings was an expected result. It presumably reflects the previously reported lack of correlation between steroid receptors and serum steroid levels [20]. The correlation of A with AR is difficult to interpret. It may partly, but not fully be explained by the dynamic reactions between the substances. The higher the levels of androstenedione, the better might be the possibilities for synthesis of AR.

The overall percentage of receptor positive findings is well comparable to that reported in the literature [1, 19]. Coexpression of steroid receptors was present for PgR and AR [17], only to a minor extent for ER and AR, contrasting with previous observations [4, 21]. It seems noteworthy in this context, that PgR was reported to be of greater prognostic value for the disease free interval and for overall survival [27]. Though our sample is small, the high correlation of tumor stage with survival may be interpreted as indicating that our sample is comparable to larger ones [12].

As for the association of AR levels with survival, a one-sided interpretation, which at 36 months reaches statistical significance (P = 0.043) could be justified in the light of previous findings [6], indicating that the presence of AR correlates

positively with survival. Since patients with positive AR findings showed better survival rates regardless of tumor stage, AR may actually add prognostic information. However, more research is needed to test this presumption with larger samples and longer time of observation.

Survival ratese were equal for groups with discordant results for ER and AR. This finding supports the hypothesis that the expression of AR does not merely reflect ER levels [6], but is a genuine indicator of differentiation. Since the ER−/AR+ group did not receive endocrine therapy, the expression of AR may be an indicator of the biological behavior of the tumor cells.

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