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Androgen Receptor Activity in Human Breast Cancer and its Relationship with Oestrogen and Progestogen Receptor Activity

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Abstract—*Androgen receptor activity was measured in tumours from 122 patients with breast cancer. Forty-two tumours (34%) possessed androgen receptors at levels varying from 17 to 210 fmol/mg cytosol protein (mean value 68). No relationship was detected between androgen receptors and menopausal status of the patients and whether or not lymph nodes were invaded with tumour at the time of biopsy. There were, however, significant positive correlations between the presence of androgen receptors and that of oestrogen ($P < 0.05$) and of progestogen receptors ($P < 0.025$). These relationships suggest that androgen receptors may be of value in predicting the hormone responsiveness of breast tumours but definitive proof of this requires clinical follow-up of the patients studied.*

INTRODUCTION

THE VALUE of oestrogen and progestogen receptors in predicting hormone responsiveness of human breast cancers is well established [1-4]. Androgen receptor activity in breast tumours has been less extensively investigated. This paper therefore describes the relationship of androgen receptors to other steroid receptors.

MATERIALS AND METHODS

Tumour was obtained from 122 patients with breast cancer. At the time of study 27 patients were premenopausal (experiencing regular menstrual periods), 90 were postmenopausal (at least 5 yr since their last regular menstrual period), four were menopausal (0-5 yr since the last menstrual period) and menopausal status was unknown in one patient. The breast cancer was obtained from the primary tumour at mastectomy (107 cases), from invaded lymph nodes during axillary clearance or sampling (13 cases) or from biopsy of local recurrent disease (two cases). The presence of malignant tumour was confirmed histologically in all samples. All material was transported on ice to a cold room and immediately processed.

The concentration of androgen receptors was determined by saturation analysis as previously described [5]. This involved incubation of a tumour cytosol overnight at 0°C with [^{3}H]R1881 (58.2 Ci/mmol) in the presence of 125 nM R5020 and varying amounts of radioinert R1881.

Progestogen receptor assays were performed on the same cytosols as were used for the androgen receptor assay. The method involved incubating the cytosol overnight at 0°C with 1 nM [^{3}H]R5020 (56.5 Ci/mmol) in the absence and presence of 1, 2, 4, 8 and 100 nM R5020.

Oestrogen receptor measurements were performed in adjacent portions of the same tumours using a method previously described [6]. Tumour cytosol was incubated overnight at 4°C with [2, 4, 6, 7-^{3}H] oestradiol-17β and varying amounts of non-radioactive oestradiol-17β.

In all receptor assays separation of free from bound steroid was by addition of dextran-coated charcoal: the bound fraction was measured by liquid scintillation counting. Concentration of receptors was determined by Scatchard analysis [7]. Activities were designated positive if in excess of 15 fmol/mg cytosol protein for androgen and progestogen receptors and greater than 5 fmol/mg cytosol protein for oestrogen receptors.

RESULTS

Androgen receptors were detected in 42 of 122 human breast cancers (34%). The incidence in primary tumours did not differ significantly from that in involved axillary lymph nodes (Table 1). Both of the local recurrences examined contained

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androgen receptors. The concentration of androgen receptor measured varied from 17 to 210 fmol/mg cytosol protein (mean value 65 fmol/mg cytosol protein) and was similar in primary tumours and involved lymph nodes (data not shown).

The presence or absence of androgen receptors in relation to menopausal status and lymph node involvement (as assessed by histological examination of axillary nodes removed at the time of primary treatment) is shown in Table 2. No significant differences were apparent in either incidence or level of androgen receptors between the various subgroups.

There was, however, a significant positive correlation between the incidence of androgen and oestrogen receptors (Table 3). Thus 40% of oestrogen receptor-positive tumours also possessed androgen receptor activity, whereas only 19% of oestrogen receptor-negative tumours did so. No significant relationship was observed between levels of androgen and oestrogen receptors in tumours which contained both activities, but the mean level of androgen receptor was higher in oestrogen receptor-negative tumours than in those with oestrogen receptors (data not shown).

There was also a significant positive correlation between the incidence of the androgen and progestogen receptor (Table 4). Thus 46% of progestogen receptor-positive tumours showed androgen receptor activity compared with 24% of the progestogen receptor-negative group. Levels of the two types of receptors were not significantly related (data not shown).

The tumours could be subdivided into eight different groups depending on the presence/absence of the three types of receptors measured (Table 5). Each combination of receptors was

Table 3. The relationship between the incidences of androgen receptors (AR) and oestrogen receptor (ER) activity

Oestrogen receptor status	AR+	AR-	(% AR+)
ER+	36	55	(40)
ER-	6	25	(19)

The incidences of the two types of receptor were positively correlated: $\chi^2 = 4.18$, $P < 0.05$.

Table 4. The relationship between the incidences of androgen receptor (AR) and progestogen receptor (PgR) activity

Progestogen receptor status	AR+	AR-	(% AR+)
PgR+	27	32	(46)
PgR-	15	48	(24)

The incidences of the two types of receptor were positively correlated: $\chi^2 = 6.5$, $P < 0.025$.

Table 1. Incidence of androgen receptor activity in human breast cancer

	No. of tumours with androgen receptors†	Total	(% positive)
Primary	35	107	(33)
Lymph node	5	13	(42)
Local recurrence	2	2	(100)

†Androgen receptor positive, >15 fmol/mg cytosol protein.

Table 2. Effects of menopausal status and lymph node involvement on incidence of androgen receptor activity

	No. of tumours with androgen receptors†	Total	(% positive)
Menopausal status			
premenopausal	6	27	(22)
menopausal	1	4	(25)
postmenopausal	34	90	(38)
Lymph node status			
involved	21	70	(30)
not involved	18	46	(39)

Differences between groups not significant by the chi square test.

Table 5. Inter-relationships between androgen receptor, oestrogen receptor and progestogen receptor activity in human breast cancers

			No.	(% of total)
AR+	ER+	PgR+	27	(22)
AR+	ER+	PgR-	9	(7)
AR+	ER-	PgR-	6	(5)
AR-	ER+	PgR+	32	(26)
AR-	ER+	PgR-	23	(19)
AR-	ER-	PgR-	25	(21)
		Total	122	(100)

represented except that no oestrogen receptor-negative, progestogen receptor-positive tumours were identified. Only six tumours contained androgen receptors alone whereas 27 had all three types of steroid receptor.

DISCUSSION

The role of both oestrogen receptors and progestogen receptors in hormone-responsive human breast cancer has been extensively evaluated. In contrast, the significance of androgen receptors in breast tumours is still uncertain. Response to certain forms of endocrine therapy is more likely in androgen receptor-positive rather than androgen receptor-negative human breast cancers [8-10], but the numbers of patients studied are small and results remain to be confirmed in larger investigations.

Although the determinations reported here have largely been performed on primary tumours from patients with early breast cancer (and therefore data on response to endocrine therapy is as yet minimal), these measurements provided the opportunity to investigate in a relatively large series the interrelationships of androgen receptors with other steroid receptors of established value.

The incidence of androgen receptors in human breast cancer of 34% and the mean level of 68 fmol/mg cytosol protein as detected in the present study are similar to the values reported by others using different methods [9, 10, 11-13]. Incidence and level were not significantly influenced by the site of tumour biopsy, menopausal status or lymph node status of the patients. A similar lack of association between these factors has been reported by others [14], although, as in the present study, there was a tendency for a higher incidence of androgen receptor activity to be observed in tumours from postmenopausal patients.

In the present study there was a significant, positive correlation between the presence of androgen receptors and that of oestrogen receptors. Others have reported a similar correlation [10, 14, 15], although it is important to note that the correlation is not absolute and that many tumours contain only one of the receptors [16].

The presence of androgen receptors also correlated with that of progestogen receptors, though, as with oestrogen receptors, there was a substantial number of tumours which contained either type of receptor alone. Because of the positive correlations between androgen receptors and both oestrogen and progestogen receptors, the presence of androgen receptors within breast cancers may also reflect hormone-dependence. However, the presence of androgen receptors in about 20% of oestrogen receptor-negative tumours, which classically are unlikely to respond to endocrine therapy, argues against androgen receptors alone being of predictive value. Nevertheless, the simultaneous presence of androgen receptors along with oestrogen and progestogen receptors (in 22% of tumours in this study) might increase the likelihood of response over that associated with tumours possessing oestrogen and progestogen receptors alone. Equally, others have suggested [9, 10] that the presence of androgen receptors might predict particularly for specific forms of endocrine therapy, especially those which affect tumour androgen levels. Clearly, clinical follow-up of the patients in this study is required to elucidate these possibilities.

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