The Breast (1996) 5, 123–126

ORIGINAL ARTICLE

Prognostic role of oestrogen, progesterone and androgen receptor in relation to patient age in patients with breast cancer

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S U M M A R Y. The recent introduction of androgen receptor (AR) status in breast cancer allows comparison of its prognostic role with that of progesterone (PgR) and oestrogen receptor (ER). In the present study of 269 breast cancer patients, a significant survival effect was found for PgR at 60 months, while ER and AR were of less importance. However, the prognostic role of ER and AR was dependent on patient age. In patients under 60 years, the effects of ER and AR were of borderline significance, i.e. slightly weaker than that of PgR. In older patients the effect of PgR was weak. The prognostic role of PgR, ER and AR appears to be age dependent.

INTRODUCTION

The prognostic effect of progesterone receptor status (PgR) and oestrogen receptor status (ER) has been extensively studied in breast cancer patients. Their role as prognostic markers is well established.[1–3] Few groups have studied the prognostic importance of androgen receptor status (AR) in breast cancer. Early work showed AR to be of no prognostic importance,[4] but later studies found borderline significance.[5,6] AR has been found to add prognostic information to that of ER,[7] but to give no additional information once the number of positive lymph nodes, ER, PgR and age have been taken into account.[8]

Although breast cancer is regarded as a heterogeneous disease,[9] which may behave differently in subgroups of patients,[10] few studies have tested for interactions between prognostic variables. Little attention has been paid to the prognostic role of ER and PgR in relation to patient age. One study did indicate a stronger effect for ER in patients over 45 years,[11] while another found an independent effect for ER and PgR in young patients and in those older than 50 years.[10] The prognostic effect of AR in relation to age has not been investigated.

The aim of this work is to compare the prognostic value of AR, PgR and ER taking account of age and adjusting for the effect of lymph node status and tumour diameter.

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MATERIALS AND METHODS

The series consists of 269 breast cancer patients with unilateral disease treated by modified radical mastectomy with axillary dissection. All types of histologically confirmed primary infiltrating carcinomas were included. The specimens were received at the Gade Institute between January 1985 and January 1988 and were followed up via data from the Norwegian Statistical Central Bureau to their death or up to January 1993, all patients having a follow-up of 60 months or longer.

Information on oestrogen, progesterone, androgen receptor concentration and age of the patients at operation was available for all patients. The greatest diameter of the primary tumour was that recorded by the pathologist and the lymph node status was histologically determined. In 36 patients information on tumour diameter was not available. In four patients information on lymph node status was missing; this included one patient for whom information on tumour diameter was also missing. The ER and PgR content was measured by the dextran-coated charcoal technique as modified by Thorsen.[12] Protein (15 fmol/mg) was chosen as the cut-off point for PgR and ER; patients with PgR and ER values less or equal to 15 fmol/mg protein being defined as negative, with higher values being positive. The dextran-coated charcoal technique, as modified by Lea, was used to measure androgen receptor content.[13] The specific ligand 10 nM[3] H-labelled methyltrienolone (R-1881) was used in this assay. To prevent unbiased preselection,[14] 43 fmol/mg

protein and 60 years of age were chosen as the cut-off point for AR and age, being the median values for patients with measured AR values in our database (309 cases). Patients with AR values less or equal to 43 fmol/mg protein were regarded as low and those greater than this as high.

Perioperative chemotherapy was given to all patients under 70 years on the day of operation and repeated on the seventh postoperative day. Tamoxifen was usually given postoperatively to lymph node positive patients with ER positive tumours, although some of these patients were randomized in a separate trial and did not receive any endocrine therapy. To test whether tamoxifen was given more frequently to patients under 60 years than those over 60 years, the files of 43 and 35 of them, respectively, were re-examined for postoperative systemic adjuvant therapy (TAa). Older patients tended to have received tamoxifen more often ($P = 0.08$).

All statistical analyses were used as programmed in BMDP.[15] The actuarial life table method was chosen using the log-rank test (Mantel–Cox) when testing for survival differences. The Cox proportional hazards model was used to compare the prognostic effect of the hormone receptor variables. This method relies on the assumption that the ratio of the death rates in groups of patients does not change with time. This proportionality assumption was checked using plots of the log minus log survival function.[15] No serious deviations from the proportionality assumption were found (not shown). Patients dying of causes other than breast cancer or breast cancer-related deaths were censured, i.e. treated as living to the time of death and then excluded.

RESULTS

Table 1 shows the distribution of patients, deaths, nodal status and tumour diameter in each age group. Patients under 60 years tended to be node positive more often than those over 60 years ($P = 0.05$), while the size distribution of tumours was similar in the two age groups.

Actuarial life table analyses

The life chart (Fig. 1) shows that the cumulative proportion surviving in the PgR positive and the PgR negative groups followed a significantly different course. Eighty-seven per cent PgR positive patients survived 60 months compared to 77% PgR negative ones. The differences between the survival curves for ER and AR were not significant. Eighty-three per cent of patients with ER-positive tumours survived compared to 80% ER negative ones. The corresponding percentages for AR were 84% and 80%.

Table 1 The distribution of patients, lymph node status, small and large tumours, breast cancer deaths and other known causes of death in each age group

	Patients ≤ 60 no. (%)	Patients > 60 no. (%)
Patients	132 (49.1)	137 (50.9)
Deaths		
Breast cancer	29 (22.0)	33 (24.1)
Other causes	2 (1.5)	15 (11.0)
Nodal status		
N–	73 (55.3)	89 (65.9)
N+	59 (44.7)	44 (33.1)
Tumour diameter		
≤ 2.5 cm	61 (55.0)	58 (47.5)
> 2.5 cm	50 (45.0)	64 (52.5)

In young patients (Fig. 2) the difference between survival curves for PgR and ER was similar, while the difference for AR was slightly less. Ninety per cent and 89% patients with PgR and ER positive tumours and 89% patients with high levels of AR survived, respectively. The corresponding figures for patients with PgR or ER negative tumours or low AR levels were 76%, 77% and 78%. In the older patients the prognostic power of all hormone receptor variables was less than in the younger. Only a weak survival difference was seen between PgR positive and negative patients, while no difference was found for ER and AR.

Proportional hazard regression analyses

Using univariate analyses without consideration of age (Table 2) PgR was the strongest variable. The effect of each variable increase when adjusted for lymph node status and tumour diameter.

PgR was also the strongest variable in patients under 60

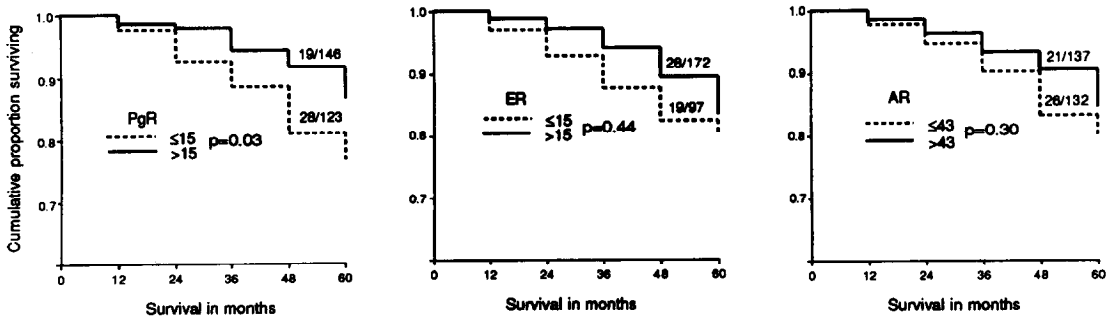

Fig. 1 The estimated cumulative proportion surviving in the total material for PgR, ER and AR.

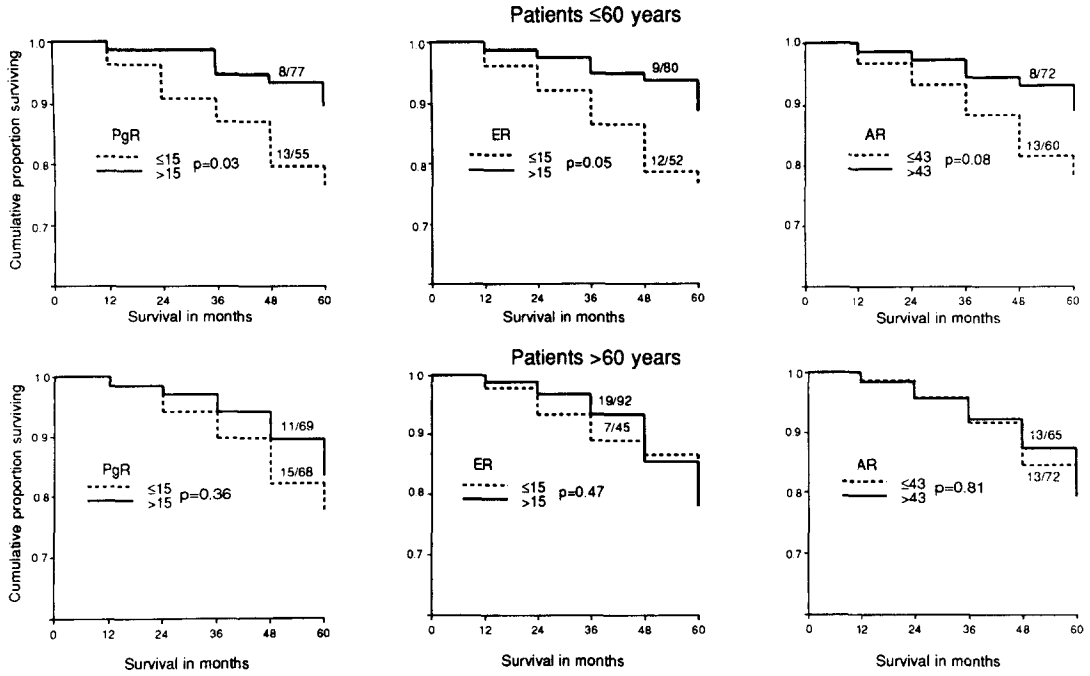

Fig. 2 The estimated cumulative proportion surviving for PgR, ER and AR in patients under 60 years and in those over.

Table 2 The relative risk of dying (RR), 95% confidence limit and *P*-value for PgR, ER and AR analysed separately unadjusted and adjusted* for tumour diameter and lymph node status using proportional hazard regression analysis

Variables	RR	95% confidence limits	*P*-value
PgR	1.9	(1.0–3.4)	0.03
PgR*	2.6	(1.3–5.1)	0.005
ER	1.3	(0.7–2.3)	0.44
ER*	2.2	(1.2–4.1)	0.02
AR	1.3	(0.8–2.4)	0.30
AR	1.7	(0.9–3.3)	0.09

Table 3 The relative risks of dying, 95% confidence limits and *P*-value for PgR, ER and AR unadjusted and adjusted* for tumour diameter and lymph node status when evaluated separately in each strata of age using proportional hazard regression analysis

Age	Variables	RR	95% confidence limits	P-value
	PgR	2.5	(1.0–6.2)	0.04
≤ 60	ER	2.3	(1.0–5.5)	0.06
	AR	2.1	(0.9–5.3)	0.09
	PgR	3.4	(1.2–9.5)	0.02
≤ 60*	ER	3.9	(1.5–10.3)	0.005
	AR	3.3	(1.2–8.8)	0.01
	PgR	1.4	(0.6–3.2)	0.37
> 60	ER	0.7	(0.3–1.8)	0.47
	AR	0.9	(0.4–2.0)	0.81
	PgR	2.6	(0.9–5.3)	0.09
> 60*	ER	1.2	(0.5–3.1)	0.69
	AR	0.9	(0.4–2.2)	0.84

years (Table 3), but ER and AR were also of importance. When adjusted for lymph node status and tumour diameter, the effects of all three variables increased to significant levels, ER becoming stronger than PgR. In patients over 60 years the effects of all variables were weak. Only PgR gained importance after adjustment. To test for any difference between the unadjusted effects of each hormone receptor variable in each strata of age, we included interaction with age in each analysis. The difference was of borderline significance for ER ($P = 0.06$), and was weaker for AR ($P = 0.15$) and PgR ($P = 0.33$).

DISCUSSION

In this report the prognostic role of AR, ER and PgR is compared in a group of women with breast cancer and after stratification for age. No consensus has been reached in the literature as to the prognostic importance of AR. Our findings are in agreement with those showing AR to be of borderline significance,[5,6] with a strength similar to that found for ER, but stronger[7] and weaker[4] associations with survival have been reported. However, the mean or median follow-up time in these works was less than 50 months, while in the present study all patients were followed up for longer than 60 months.

In the present study AR and ER gave weaker information than that of PgR in the whole group. This is not in agreement with an early report showing ER positivity to be associated with a prolonged disease-free interval, while no such association was found for PgR or AR.[4] Our results are more in agreement with a report showing that AR did not improve prediction of survival when the number of positive lymph nodes, ER and PgR had been accounted for.[8]

The present report shows that the effect of PgR, ER and AR are dependent on patient age at operation, all hormone receptor variables being stronger in patients under 60 years. The strongest age dependency was found for ER followed by AR and PgR. Previous works have not focused on the interaction with age. Papatestas et al[10] showed that PgR and ER gave information on disease-free survival in patients both under and over 50 years, while Shek et al[11] showed a weaker effect of ER level in women younger than 45 years than in those older. These diverging results suggest that division into two groups according to menopausal status or age is an over simplification, and that the relation between hormone receptors and survival should be examined in smaller age groups in a larger series. Using 60 years as the cut-off point the lower age group contains some postmenopausal patients. No consensus has been reached as to the role of PgR and ER in relation to menopausal status. Our results are in agreement with those showing a stronger effect for PgR[16] and ER[17] in premenopausal women. We are thus not able to exclude an effect for PgR and ER in postmenopausal patients as shown in other works.[18–20] This may also explain why Bryan et al[7] found an effect for AR in postmenopausal patients only.

In the present work the prognostic power of hormone receptors and their age dependency became even stronger after consideration of lymph node status and tumour diameter. This is in agreement with a previous report showing the stage disease influences the relation between hormone receptors and survival.[21] We therefore analyzed their role after stratifying for lymph node status and tumour diameter in separate analyses. The effects were stronger in lymph node positive patients and in those with tumours less or equal to 2.5 cm (not shown).

Results from the meta-analyses of the Early Breast Cancer Trialists' Collaborative Group, including 75 000 women, have reported the treatment effect of tamoxifen on recurrence-free survival to be present both in young and old patients, but the effect was significantly stronger in the old age group.[22] The effect on survival was less, and there was no important difference in the tamoxifen effect at different ages. In our material tamoxifen had been given to lymph node positive patients with ER positive tumours. Although older patients tended to receive tamoxifen treatment more frequently than young ones, the survival difference between hormone receptor positive and negative patients was more pronounced in young patients. It seems unlikely therefore that the better prognosis seen in young receptor positive patients was due to treatment differences.

Acknowledgement

Our thanks are due to Oscar A. Lea who did the measurements of the androgen receptor content (deceased 1990).

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