Prognostic role of oestrogen and progesterone receptors in patients with breast cancer: relation to age and lymph node status

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Abstract

Aims—To consider the prognostic role of oestrogen receptor and progesterone receptor status in relation to the age at surgery, length of follow up and lymph node status.

Methods—The study population comprised 977 patients with histologically confirmed breast carcinoma, with a median follow up of nine years. The actuarial life table method was used to test for survival differences. The Cox proportional hazard model was used to test for interaction effects between each hormone receptor and age, lymph node status and length of follow up. As the analysis involved multiple subgroups, significance was set at the 1% level (p < 0.01).

Results—When the patients were subdivided into groups according to lymph node status and age, progesterone and oestrogen receptor status predicted prognosis in middle aged (46–60 years) patients with lymph node positive breast cancer. Their prognostic effect in this subgroup, however, was restricted to the first five years after surgery. Progesterone receptor status was the strongest predictor of outcome.

Conclusion—The prognostic power of oestrogen and progesterone receptor status varies depending on age, lymph node status and length of follow up after surgery.

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Despite the trend towards the use of adjuvant therapy in most patients with breast cancer,[1] prognostic factors are still needed to identify patients at high, and low, risk of recurrence and, perhaps most importantly, patients who are unlikely to benefit from a particular treatment.[2] Several new markers have been introduced to identify these patients, but none has yet improved our ability to determine survival.[3] The search for better markers has, to some extent, led to less interest in traditional histopathology.[4] Intrinsic factors such as c-erbB-2, c-myc, DNA index, and S-phase fraction have, however, been shown to lose prognostic power after inclusion of histological grade in multivariate analysis for survival.[5] In contrast to the more recent prognostic indica-

tors, oestrogen and progesterone receptor status are well established markers,[3] and they were included in the 1992 St Gallen recommendations for the adjuvant treatment of breast cancer.[1]

Interactions with other factors have been shown to have an impact on the prognostic role of oestrogen and progesterone receptor status. Previous reports have shown that the hormone receptors are stronger factors in lymph node positive than negative patients[6-8] and are more important in predicting short rather than long term prognosis.[9-11] Their effects in relation to menopausal status have also been studied, but no consensus has been reached as to whether their effect is stronger in pre-[8 12] or postmenopausal women.[13-15] This could result from different definitions of menopausal status and suggests that oestrogen and progesterone receptor status should be examined in middle aged patients separately.

Few reports have focused on the effect of oestrogen and progesterone receptor status in relation to age. Shek *et al*[16] showed a weak effect for oestrogen receptor status in patients aged 45 years or less, whereas the strongest effect was found in those between 45 and 54 years of age. We have shown that oestrogen, progesterone and androgen receptor status are more important in predicting five year survival in patients aged 60 years or less than in those over 60.[17] The association with age became even stronger after consideration of lymph node status and tumour diameter. As this study included 269 patients only, it did not permit further subdivision according to age. By excluding the need for androgen receptor status in the present study we could increase the study population to 977 and follow up to about nine years.

Based on these considerations we hypothesise that the prognostic importance of oestrogen and progesterone receptor status should be examined in middle aged patients separately, taking lymph node status and length of follow up into consideration. Identification of interactions between these variables would allow these well established prognostic markers to be used more precisely in patients with breast cancer.

Methods

The study population comprised 977 patients with unilateral breast cancer treated by modified radical mastectomy with axillary dissection. All types of histologically confirmed infil-

trating carcinoma were included. The specimens were received at this Institute between January 1974 and January 1989 and patients were followed up via data from the Norwegian Statistical Central Bureau until death or to January 1994.

All patients under 70 years of age received perioperative chemotherapy. Between 1976 and 1981, 330 patients under 75 years of age were randomised in a trial to receive different courses of CMF/CMFP (cyclophosphamide, methotrexate, 5-fluorouracil/prednisolone). Before 1983, patients did not receive tamoxifen postoperatively. Thereafter, as a general rule, tamoxifen was given daily postoperatively for two years in lymph node positive patients with oestrogen receptor >10 fmol/mg. As we do not have detailed information on tamoxifen treatment, we have re-analysed our findings in lymph node positive patients who underwent surgery before and after 1983. In both periods oestrogen and progesterone receptor status exerted the strongest effect in middle aged patients (data not shown). Thus, this observation indicates that any age dependent effect of oestrogen and progesterone receptor status is not a result of tamoxifen treatment. As part of the primary treatment an unknown proportion of patients received postoperative radiotherapy.

Information on oestrogen and progesterone receptor status and age at surgery was available for all patients. As information on progesterone receptor concentration was not available before January 1976, only 852 patients were included in this arm of the study. As information on lymph node status was missing in some cases, the analyses were based on 965 and 843 patients for oestrogen receptor and progesterone receptor, respectively, when lymph node status was included. When adjusting for tumour diameter only patients with known tumour diameter were included in the analyses: 853 and 741 cases for oestrogen receptor and progesterone receptor, respectively. Median follow up was 108 (61–238) and 104 (61–207) months for oestrogen receptor and progesterone receptor, respectively. Oestrogen receptor and progesterone receptor content was measured by the dextran coated charcoal technique as described by Thorsen.[18] All analyses were done in a single laboratory using the same method, eliminating the problem of interlaboratory differences; 15 fmol/mg protein was chosen as the cut-off point for oestrogen receptor and progesterone receptor, and 60 years was chosen as the upper cut-off point for age, as used in our previous study.[17] Pilot studies showed that the effect of oestrogen and progesterone receptor status differed in patients aged 45 years or less compared with those between 45 and 60 years of age; therefore, 45 years was chosen as the lower cut-off point for middle aged patients. Changing this cut-off point for age from 45 to 50 years gave a similar pattern for oestrogen receptor and progesterone receptor as prognostic variables. All statistical analyses were used as suggested by Dixon.[19] Patients dying of causes other than breast cancer were censured—that is, treated as living until death and then excluded. As the

analysis involves multiple subgroups, significance was set at the 1% level (p < 0.01). The actuarial life table method was chosen, using the log rank test (Mantel-Cox), to test for differences in survival. The Cox proportional hazard model was used to estimate the relative risk of dying and interactions between each hormone receptor and age, lymph node status and length of follow up. This model relies on the assumption that the ratio of death rates in groups of patients does not change with time. To assess whether the effect of oestrogen receptor and progesterone receptor differed during the first (first five years) compared with the last (next five years) period, a time dependent variable was designed for each hormone receptor and tested for significance. The proportionality assumption was checked in each five year period using plots of the log minus log survival function.[19] No serious deviations from the proportionality assumptions were found (data not shown).

Results

Overall, a weak survival advantage was seen for oestrogen receptor positive patients (table 1). When stratified according to lymph node status, oestrogen receptor status was significant in lymph node positive patients only. A weak effect was seen for oestrogen receptor status in young and old patients, while no survival difference was found between oestrogen receptor positive and oestrogen receptor negative middle aged women.

On stratifying according to lymph node status and age simultaneously (fig 1), oestrogen receptor status tended to give survival information in middle aged and in young lymph node positive patients, oestrogen receptor negative patients being at higher risk than oestrogen receptor positive ones. The difference between the groups declined after five years. In the middle aged lymph node negative group, however, more deaths were seen in patients with oestrogen receptor positive tumours than in those with oestrogen receptor negative ones after five years of follow up.

Using the Cox proportional hazard model in each five year period (table 2), oestrogen receptor status was significant in lymph node positive patients in the first five years after surgery. It showed a significant reverse of effect in the second period in middle aged patients, those with oestrogen receptor positive tumours having a 3.3-fold higher risk of dying than oestrogen receptor negative patients. When testing for interactions a weak difference in effect was seen between the periods overall (p = 0.07). A significant difference was not seen in effect between the nodal strata in the first or last period (p > 0.25) or between the age groups in the first period (p > 0.33). In the last period a significantly different effect was found between middle aged and elderly patients (p = 0.008), while that between young and middle aged patients was weaker (p = 0.09).

When patients were grouped according to both age and lymph node status (table 2) oestrogen receptor status was significant in middle aged lymph node positive patients during the

Table 1   Number (%) of patients dying of oestrogen receptor positive or negative breast cancer, stratified according to lymph node status and age at operation (years), by means of actuarial survival analyses estimating 10 year survival. The p values were derived using the log rank test

Subgroup	Oestrogen receptor status	Deaths/total	(%)	p value
Total	Positive	156/579	(26.9)	0.19
	Negative	120/398	(30.2)	
Lymph node negative	Positive	53/312	(17.0)	0.73
	Negative	43/239	(18.0)	
Lymph node positive	Positive	99/262	(37.8)	0.003
	Negative	76/152	(50.0)	
Age (years)				
≤45	Positive	15/73	(20.5)	0.13
	Negative	25/80	(31.3)	
46–60	Positive	50/165	(30.3)	0.98
	Negative	42/149	(28.2)	
>60	Positive	91/341	(26.7)	0.19
	Negative	53/169	(31.4)	

first five years of follow up only. Oestrogen receptor status also tended to have an effect in young, lymph node positive patients. After five years, middle aged, lymph node negative patients with oestrogen receptor positive tumours had a fivefold higher risk of dying than those with oestrogen receptor negative ones. This effect, however, was not significant. Adjusting for tumour diameter gave similar results (data not shown).

Although more progesterone receptor positive patients survived for 10 years than progesterone receptor negative ones, the uncertainty was great (table 3). However, this difference was significant in lymph node positive patients and in middle aged patients. No effect was found in node negative nor in young and old patients.

A significant survival difference was found for progesterone receptor status in middle aged, lymph node positive patients, but this difference declined after five years (fig 2). A weaker effect of borderline significance was also found in elderly, lymph node positive patients. No effect was found in any other subgroup.

Using Cox proportional hazard regression analysis (table 4), progesterone receptor status was significant in the first five years of follow up overall. A reversed effect of borderline significance was found in the second five year

Table 2   Relative risk (RR) of dying and 99% confidence interval (CI) in patients with oestrogen receptor negative versus oestrogen receptor positive tumours overall and in subgroups of patients stratified according to lymph node status and age at operation (years) in the first and second five years of follow up using the Cox proportional hazard regression model. The p values were derived using the Wald test

	First five years			Second five years		
	RR	CI	p value	RR	CI	p value
Total	1.4	0.9–2.0	0.04	0.8	0.5–1.5	0.42
Nodal status						
Negative	1.3	0.7–2.5	0.35	0.8	0.3–2.0	0.51
Positive	1.8	1.1–2.8	0.0009	1.0	0.5–2.3	0.92
Age						
≤45	1.9	0.7–5.5	0.11	1.2	0.3–4.9	0.77
46–60*	1.6	0.8–3.1	0.07	0.3	0.1–1.0	0.01
>60	1.2	0.7–2.0	0.42	1.5	0.6–3.5	0.24
Nodal status/age						
Negative/≤45	1.9	0.2–16.2	0.44	3.5	0.2–61.9	0.26
Negative/46–60	0.9	0.2–3.2	0.76	0.2	0.0–1.2	0.02
Negative/>60	1.6	0.7–3.6	0.17	1.4	0.4–5.1	0.46
Positive/≤45	3.1	0.9–11.1	0.02	0.7	0.08–5.6	0.61
Positive/46–60	2.5	1.2–5.7	0.002	0.7	0.2–2.6	0.43
Positive/>60	1.3	0.6–2.5	0.40	2.1	0.7–6.5	0.10

*The difference in effect between the first five years compared with the second five years of follow up is significant (p < 0.01).
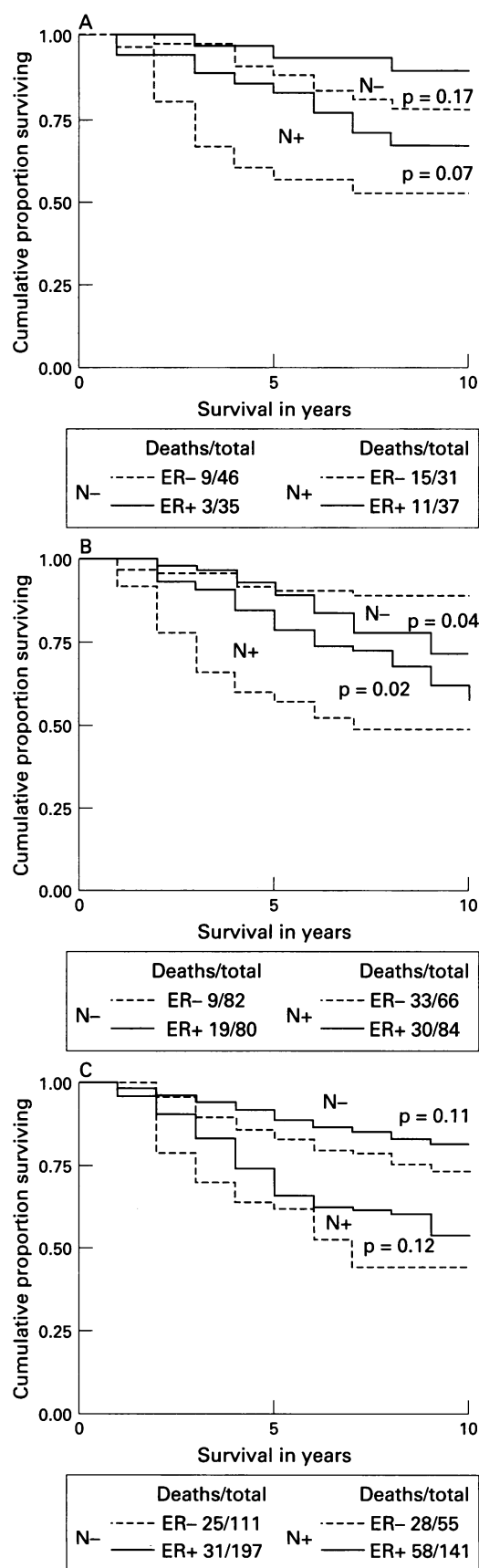

Figure 1   Estimated cumulative proportion of patients surviving, after stratification according to age [(A) ≤45 years; (B) 46–60 years; (C) > 60 years] and lymph node status, as predicted by oestrogen receptor (ER) status.

period. In the first five year period progesterone receptor status was significant in lymph node positive and in middle aged patients. This was not the case for the second five year period.

Table 3   Number (%) of patients dying of progesterone receptor positive or negative breast cancer, stratified according to lymph node status and age at operation (years), by means of actuarial survival analyses estimating 10 year survival. The p values were derived using the log rank test

Subgroup	Progesterone receptor status	Deaths/total	(%)	p value
Total	Positive	105/419	(25.1)	0.06
	Negative	129/433	(29.8)	
Lymph node negative	Positive	36/224	(16.1)	0.99
	Negative	41/256	(16.0)	
Lymph node positive	Positive	67/190	(35.3)	0.0006
	Negative	85/173	(49.1)	
Age (years)				
≤45	Positive	20/80	(25.0)	0.98
	Negative	13/54	(24.1)	
46–60	Positive	25/122	(20.5)	0.009
	Negative	52/154	(33.8)	
>60	Positive	64/225	(28.4)	0.66
	Negative	60/217	(27.6)	

When testing for interactions a significant difference in effect was seen between the periods overall (p = 0.001). In the first five year period the prognostic importance of progesterone receptor status differed in lymph node positive and negative patients but the difference did not reach significance (p = 0.04). A significantly different effect was found between middle aged and elderly patients (p = 0.008), whereas that between young amd middle aged patients was weaker (p = 0.08). Thus, with regard to length of follow up, lymph node status and age the effect of progesterone receptor status differs more than that of oestrogen receptor status.

As for oestrogen receptor, progesterone receptor status was significant in middle aged, lymph node positive patients during the first five years of follow up only (table 4). A weaker effect of borderline significance was found in elderly, lymph node positive patients. Progesterone receptor status was of no importance after five years of follow up, irrespective of age and lymph node status. Adjusting for tumour diameter gave a similar result in middle aged and elderly patients in both nodal groups (data not shown). Because of small numbers it was not possible to adjust further for tumour diameter in the youngest age groups.

Considering middle aged, lymph node positive patients only (fig 3), the combined effect of

Table 4   Relative risk (RR) of dying and 99% confidence interval (CI) in patients with progesterone receptor negative versus progesterone receptor positive tumours overall and in subgroups of patients stratified according to lymph node status and age at operation (years) in the first and second five years of follow up using the Cox proportional hazard regression model. The p values were derived using the Wald test

	First five years			Second five years		
	RR	CI	p value	RR	CI	p value
Total*	1.7	1.1–2.6	0.0008	0.6	0.3–1.2	0.08
Nodal status						
Negative	1.2	0.6–2.5	0.51	0.7	0.2–1.9	0.33
Positive*	2.4	1.5–4.1	< 0.0001	0.7	0.3–1.7	0.34
Age						
≤45	1.4	0.5–4.3	0.45	0.5	0.1–2.9	0.34
46–60*	3.7	1.5–9.1	0.0002	0.7	0.2–1.8	0.29
>60	1.3	0.7–2.1	0.27	0.7	0.3–1.8	0.29
Nodal status/age						
Negative/≤45	5.6	0.3–97.3	0.13	0.6	0.0–11.1	0.63
Negative/46–60	1.1	0.3–5.1	0.85	0.9	0.2–5.0	0.86
Negative/>60	1.0	0.4–2.3	0.92	0.6	0.1–2.5	0.31
Positive/≤45	1.2	0.3–4.8	0.69	0.3	0.02–4.3	0.22
Positive/46–60*	6.9	2.0–23.6	0.0001	0.7	0.2–2.5	0.43
Positive/>60	1.9	0.9–3.7	0.02	1.1	0.3–3.9	0.80

*The difference in effect between the first five years compared with the second five years of follow up is significant (p < 0.01).
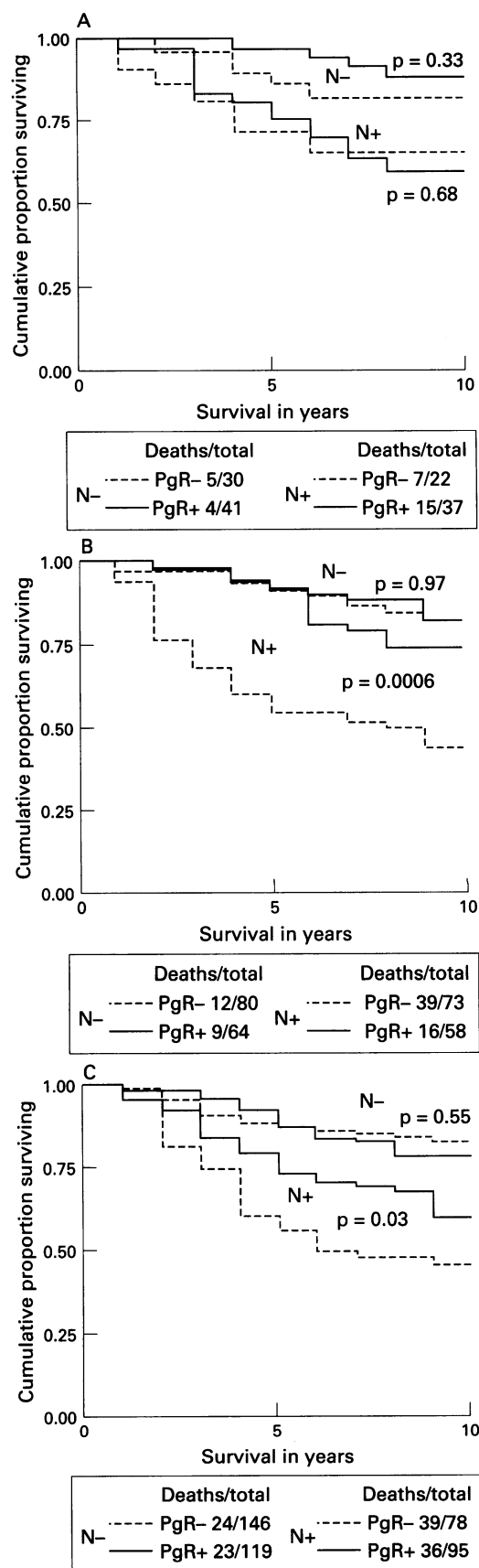

Figure 2   The estimated cumulative proportion of patients surviving, after stratification according to age [(A) ≤45 years; (B) 46–60 years; (C) >60 years] and lymph node status, as predicted by progesterone receptor (PgR) status.

oestrogen and progesterone receptor status was a good predictor of prognosis in the first five years of follow up. Patients with progesterone receptor negative/oestrogen receptor negative
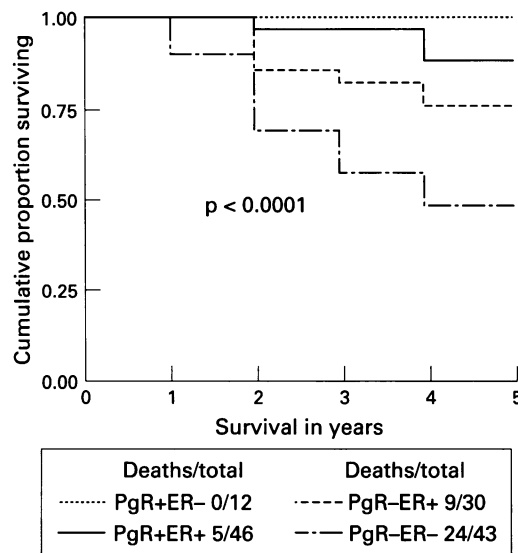
Figure 3 *The estimated cumulative proportion of middle aged, lymph node positive patients surviving as predicted by the combined effect of progesterone (PgR) and oestrogen (ER) receptor status in the first five years of follow up.*

Table 5 *Regression coefficients for oestrogen and progesterone receptor, relative risk (RR) of dying, 99% confidence interval (CI), and p values, derived from the Wald test, in middle aged, lymph node positive patients*

Receptor	Regression coefficient		p value
	RR	CI	
Oestrogen	−0.61	1.8 (0.8–4.5)	0.08
Progesterone	−1.72	5.6 (1.6–20.0)	0.0005

tumours faired poorly, while the best prognosis was found in progesterone receptor positive/oestrogen receptor positive and in progesterone receptor positive/oestrogen receptor negative patients. No deaths were recorded for the latter patients.

When analysing both receptors simultaneously in middle aged, lymph node positive patients in the first five years of follow up using Cox proportional hazard regression analysis (table 5), progesterone receptor status was the strongest factor. Additional information was, however, given by oestrogen receptor status, but because of the relatively small number of patients, the uncertainty of the estimate was great. Middle aged, lymph node positive patients with oestrogen receptor negative/progesterone receptor negative tumours had a 10.3-fold higher risk of dying than oestrogen receptor positive/progesterone receptor positive ones.

Discussion

The prognostic effect of progesterone receptor status was significant in lymph node positive patients only, which is in agreement with recent findings,[7][8][20] but it is in contrast to those of Pichon et al.[21] The interaction between progesterone receptor and lymph node status was significant in this study, indicating that patients should be stratified by lymph node status when evaluating the effect of progesterone receptor. We have reported previously that progesterone receptor status is an important predictor of

short term prognosis in both lymph node positive and negative patients. A stratified analysis, however, was not done.[22] Although the present study also supports previous findings showing that oestrogen receptor status is more important in lymph node positive than in lymph node negative patients,[6][7][14] we agree with Winstanley et al[23] that the interaction between oestrogen receptor and lymph node status does not reach significance.

Spyratos et al[10] found that progesterone receptor status was an independent prognostic marker of metastasis free survival at two and five years, but lost its significance at 10 years. We found that oestrogen receptor status affects prognosis in the short term, which is in agreement with other reports.[6][9][15][23] In the present series the difference between the effects in the two periods was significant for progesterone receptor, while for oestrogen receptor this difference was of borderline significance only. The loss of effect of oestrogen receptor in the second five year period in middle aged, lymph node negative patients contributed to the overall loss of effect in this period and also to the loss of effect in lymph node negative patients overall. Other authors have also reported a lack of benefit for oestrogen receptor positive women five years after surgery.[6][24][25] These data suggest that regression analysis should be limited to relatively short periods. Indeed, even in the short periods used in our study the relative risk of progesterone receptor negative and positive patients may change.[22]

In a series including 269 patients we found that progesterone receptor, oestrogen receptor and androgen receptor status were all stronger predictors of five year survival in patients aged ≤60 years than in those over 60.[17] The present study confirms these findings for progesterone receptor and oestrogen receptor, but showed that progesterone receptor status is an important predictor of prognosis in middle aged patients only. The effect of oestrogen receptor status was stronger in young and middle aged patients than in elderly ones, but the difference was not significant (p = 0.22). Thus, the effect of progesterone receptor varies with age. Although many reports have shown that the predictive effect of progesterone and oestrogen receptor varies with menopausal state, the pattern of divergence is unclear. This may be because the behaviour of cancer is different in young, middle aged and elderly patients, making the choice of a cut-off age critical in pre- and postmenopausal women.

The present study also shows that when lymph node status and length of follow up are considered, oestrogen receptor and progesterone receptor status have a significant effect on survival in middle aged, lymph node positive patients only during the first five years of follow up. Most of these middle aged patients may characteristically be in a state of hormonal flux as a result of a decrease in circulating oestrogen concentrations. The results reported here lend support to the hypothesis that hormones influence the biological behaviour of breast cancer.[26][27] This influence seems to stronger in lymph node positive than lymph node negative

patients. The loss of effect of oestrogen receptor status seen in lymph node negative patients lends further support to the hypothesis that breast cancer behaves differently depending on lymph node status. We therefore disagree with a Nordén *et al*,[28] who reported that it is unnecessary to stratify patients according to lymph node status.

Although it is well known that established biological prognostic factors such as steroid hormone receptors show patterns of associations that vary with age,[29] the prognostic value of oestrogen receptor and progesterone receptor in different age groups, when stratified by nodal status, does not seem to have been reported previously. These results require confirmation in a larger series. However, it is important to stress that in lymph node positive patients who underwent surgery before and after 1983, oestrogen receptor and progesterone receptor were the strongest predictors of prognosis in middle aged patients during the first five years in both periods.

In conclusion, this report shows that age, lymph node status and length of follow up are important for the evaluation of oestrogen receptor and progesterone receptor as prognostic variables. It has been stressed that new factors should be combined with traditional ones in multivariate analyses and included in indexes used to evaluate prognosis in patients with breast cancer.[30]

If oestrogen and progesterone receptor status are to be used to predict survival of patients with breast cancer, then different criteria (indexes) should be used in different age and lymph node groups.

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