The association of cytosol oestrogen and progesterone receptors with histological features of breast cancer and early recurrence of disease

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Summary Two hundred and eighty-eight primary breast tumours were examined for the presence or absence of oestrogen (RE_c) and progesterone (RP_c) receptors. Analysis has shown a relative interdependence between the steroid receptor status of primary breast cancer and other prognostic variables such as histological grade, lymphocytic infiltration and tumour elastosis. There were significant associations between epithelial cellularity, stromal fibrosis and the value of RE_c in those tumours in which the receptor was present. Cellularity and fibrosis were unrelated to the presence or absence of oestrogen receptor. By contrast, neither the presence or absence nor the value of RP_c could be related to cellularity or fibrosis. The value of RE_c and RP_c analysis as an indicator of prognosis was examined in a sub-group of 175 patients receiving no additional treatment following mastectomy. Overall relapse-free survival (RFS) was no different for those patients with receptors compared to those without them (RE_c $P=0.11$, RP_c $P=0.7$). There was no difference in RFS of receptor positive and negative tumours when the axillary node status was taken into account.

Increased recognition of the importance of selective hormone binding in initiating steroid action in target tissues has led to the study of oestrogen and progesterone binding by human breast cancer. Though the receptor content of the primary tumour is reported to be independent of factors such as tumour site or size, age of patient or degree of axillary node involvement (Knight *et al.*, 1977) it is not known to what degree tumour differentiation is under endocrine control. Studies linking receptors and hormone-dependent proteins with morphological and clinical features may help clinicians to recognise tumours which are hormone-sensitive. In early studies of this nature there was no consistent relationship between specific histopathological features of the tumour and either the presence or the value of RE_c (Sander, 1968; Korenman & Dukes, 1970; Johansson *et al.*, 1970; Feherty *et al.*, 1971; Wittliff *et al.*, 1971; LeClercq *et al.*, 1973; Terenius *et al.*, 1974; Aspergren & Hakansson, 1974). However, in some of these studies numbers were small and methods of RE_c analysis and morphological examination were inconsistent. More recent studies have shown that RE_c may be closely related to tumour grade (Maynard *et al.*, 1978; Martin *et al.*, 1979b;

Rasmussen *et al.*, 1981; Thoresen *et al.*, 1981), to the histological type and degree of lymphocytic infiltration of primary tumour (Rosen *et al.*, 1975) and to the presence or absence of elastosis in the tumour stroma (Masters *et al.*, 1976). Similar links have been recognised between the progesterone receptor (RP_c) and histological grade and elastosis (Martin *et al.*, 1979b; Rolland *et al.*, 1980), but a relationship between RP_c and other aspects of tumour morphology has not been reported.

Most investigators who have studied the relationship between RE_c and freedom from recurrence and survival, have suggested that an earlier recurrence and shorter survival may be expected in those patients who lack RE_c in their primary tumour, although data vary as to which patients obtain the greatest benefit (Knight *et al.*, 1977; Maynard *et al.*, 1978; Bishop *et al.*, 1979; Cooke *et al.*, 1979; Allegra *et al.*, 1979; Forrest *et al.*, 1980; Westerberg *et al.*, 1980; Croton *et al.*, 1981). As the RE_c is said to be independent of other prognostic variables in breast cancer, the measurement of this receptor has been advocated as a means of selecting patients likely to benefit most from systemic adjuvant therapy (Cooke *et al.*, 1980). By contrast, Hilf and his colleagues (1980) were unable to confirm that RE_c has any beneficial effect on the disease process.

Similar studies which link the presence or absence of RP_c to relapse-free survival (RFS), have also produced conflicting results (Pichon *et al.*, 1980; Allegra *et al.*, 1979; Kinne *et al.*, 1981) and the role

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of this receptor as a prognostic factor in breast cancer remains uncertain.

The objectives of this single centre study were twofold: to test the hypothesis that the presence or absence of RE_c and RP_c is a reflection of certain morphological features of the tumour, some of which are of prognostic significance in their own right and to investigate the role of RE_c and RP_c as indicators of early recurrence.

Materials and methods

Oestrogen and progesterone receptor assay

Samples of histologically proven primary tumours from women with breast cancer were studied. Portions for oestrogen (RE_c) and progesterone (RP_c) receptor measurement were selected at the time of surgery by the pathologist who received tissue for frozen section. They were stored in liquid nitrogen until required for analysis, and then homogenised and centrifuged. The receptor content of the cytosol was measured by incubation with either tritiated oestradiol in the presence or absence of diethyl-stilboestrol as a competitor for specific oestrogen receptor sites, or tritiated R5020 and radio-inert R5020, a synthetic progestin, for specific progesterone receptor sites. Non-receptor bound [^{3}H]-hormone was separated from hormone bound to receptors by adsorption on to Dextran-coated charcoal (DCC). The activity of the receptor-bound radio-labelled hormone remaining in the supernatant was measured in a scintillation counter and the data analysed according to Scatchard (1949). Values >5 fM mg^{-1} for RE_c and >15 fM mg^{-1} for RP_c of cytosol protein were regarded as positive (Barnes *et al.*, 1977; Skinner *et al.*, 1980). Negative results from tumours where the cytosol protein was <0.7 mg ml^{-1} were not accepted as valid and were excluded from the study.

Histology

The pathological features of 288 unselected primary malignant breast tumours were reviewed retrospectively by one pathologist who was unaware of the receptor status. His observations were based on the examination of routine paraffin wax embedded sections stained with haematoxylin and eosin and sections stained for elastic tissue with Miller's Victoria blue and Van Geison stain. The following pathological observations were made: the maximum diameter, the nature of the margin (circumscribed or stellate), and the histological type of the primary tumour. The grade of infiltrating duct tumours was assessed on a scale of 1 (well-differentiated) to 3 (poorly-differentiated) taking into account tubular differentiation, nuclear

pleomorphism and mitotic activity according to the method recommended by Scarff & Torloni (1968) which is essentially that of Bloom & Richardson (1957). The degree of lymphoid reaction in and around the primary tumour was evaluated on a scale of 1 (slight or none) to 3 (marked), and the epithelial cellularity of the middle and the edge of the tumour, the stromal reaction or fibrosis within the tumour and the degree of elastic tissue formation within the stroma were similarly assessed. This is a semi-quantitative visual assessment based on the experience of the pathologist.

Assessment of recurrence

The relationship of the RE_c and RP_c status to the development of early recurrence of the disease was studied in a subgroup of 175 patients with operable disease ($T_{1-3}N_{0-1}M_0$). Each had a Patey modified radical mastectomy. After histological examination of the axillary nodes, the patients were classified into three groups: those with no nodes containing tumour; those with 1–3 nodes containing tumour; and patients with 4 or more nodes containing tumour. Patients with bilateral tumours, or distant metastases and those receiving adjuvant hormone or cytotoxic therapy were excluded from this part of the study.

The patients were examined one month after operation, then every 6 weeks for 2 years and thereafter annually. Local recurrence and nodal disease was confirmed where possible by biopsy while distant bone and visceral metastases were diagnosed on unequivocal radiological evidence.

Statistical methods

The Chi-squared test was used to test for association between histological features and receptor status in $r \times c$ contingency tables. The relationship between RE_c and RP_c content and degrees of cellularity, fibrosis, lymphocytic infiltration, elastosis and histological grade was examined by means of the Kruskal Wallis non-parametric one-way Analysis of Variance (ANOVA).

For studies of RFS time-based curves were computed by actuarial methods and compared by the log-rank test (Peto *et al.*, 1977).

Results

Receptor status and age

The subgroups of patients analysed in relation to histology (288) or recurrence of disease (175) were shown statistically to be similar in composition in terms of age, menopausal status, and frequency of receptor-positive tumours, to an overall group of

523 consecutive patients with breast cancer studied in a 4-year period, but in whom complete histological or follow-up data was not available. Sixty per cent of the patients had tumours containing RE_c and 40% RP_c. Fifty-three per cent of premenopausal and 62% of postmenopausal patients possessed RE_c. Absolute values of RE_c showed a statistically significant association with age, being higher in older women and confirming a previous observation from our laboratory (Skinner et al., 1980). For RP_c the proportions of receptor-positive premenopausal (43%) and postmenopausal (38%) patients were similar and age had no influence on the value of RP_c.

Receptor status and pathological parameters

The morphological and histological features of 288 primary tumours were studied in relation to both the receptor status, and in receptor-positive tumours, to the value of RE_c and RP_c. There was no relationship between the presence or absence of RE_c and RP_c and either the diameter of the tumour or whether the margins were circumscribed or infiltrative. The relationship between receptor status and histological type of tumour is shown in Table I. All of the tubular carcinomas contained RE_c and RP_c, and 70% of the infiltrating lobular carcinomas contained RE_c. However, the numbers of some types of tumour were too small to permit statistical evaluation.

Table I Relationship of histological type of primary tumour to oestrogen and progesterone receptor status

Histological type	RE_c No. positive	(%)	RP_c No. positive	(%)
Intraduct	5/9	(55)	3/9	(33)
Infiltrating duct*	148/248	(60)	100/233	(43)
Infiltrating papillary	1/1	(100)	—	—
Mucoid	5/8	(63)	1/8	(13)
Medullary	0/3	(0)	0/3	(0)
Infiltrating lobular	7/10	(70)	4/10	(40)
Tubular	7/7	(100)	5/5	(100)
Sarcoma	0/2	(0)	0/2	(0)

*All grades.

Histological grade

RE_c was measured in 157 and RP_c in 142 infiltrating duct carcinomas in which grade was assessed. There was a highly significant association between the presence or absence of both types of receptor and the histological grade (RE_c vs. grade $P = 0.0004$; RE_c vs. grade $P = 0.0001$). RE_c and RP_c occurred most frequently in grade 1 (well-differentiated) tumours whereas there were relatively few receptor-positive tumours in grade III (poorly-differentiated) (Figure 1). In receptor-positive tumours there was no association between grade and value of either RE_c ($P = 0.6$) or RP_c
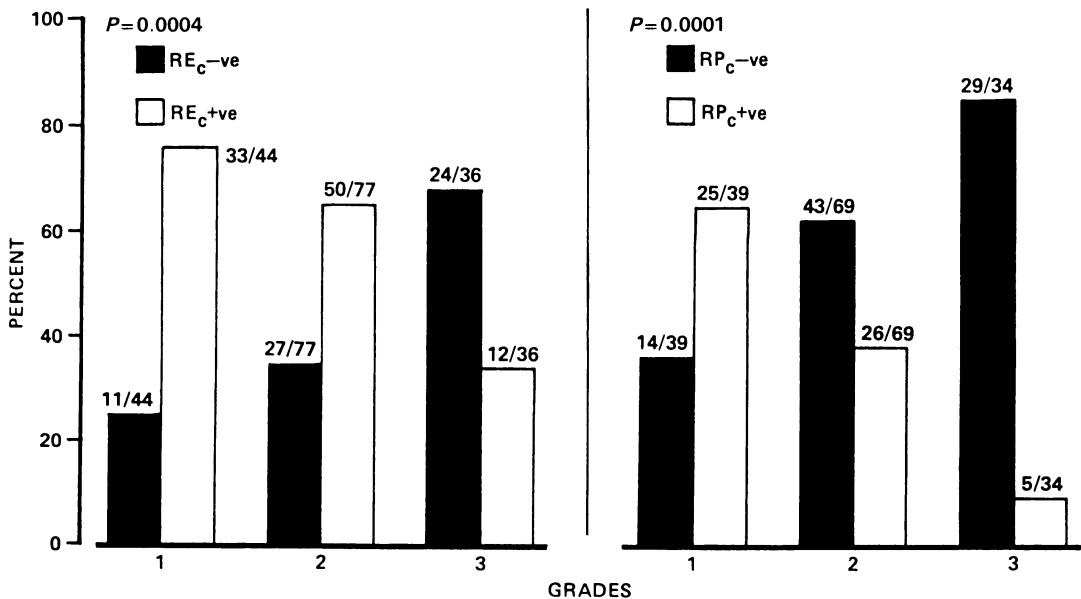

Figure 1   Relationship of RE_c and RP_c to grade of infiltrating duct tumours.

($P = 0.8$). Specific types of tumours, e.g. lobular, medullary and tubular, were not graded and were excluded from this section.

Cellularity and fibrosis

In those tumours in which receptors were found there was a significant association between cellularity, both at the centre and at the edge of the tumour, and the value of RE_c ($P < 0.0001$) (Figure 2) although cellularity was unrelated to the presence or absence of RE_c (RE_c *vs.* cellularity edge, $P = 0.7$; centre, $P = 0.1$). Tumour cellularity was not related to either the value of RP_c (edge, $P = 0.2$; centre, $P = 0.3$), or to the presence or absence of this receptor (RP_c *vs.* cellularity centre, $P = 0.5$; edge, $P = 0.8$). In RE_c-positive tumours there was an inverse association between the degree of stromal fibrosis and value of RE_c, those tumours with most fibrosis containing lowest values of receptor ($P < 0.0001$) although there was no association between the degree of fibrosis and the presence or absence of RE_c ($P = 0.2$). Fibrosis was not related to either presence or the value of RP_c ($P = 0.2$, $P = 0.5$).

Figure 2 RE_c values related to cellularity assessed at the tumour edge. Median value and upper and lower quartiles shown.

Elastosis

RE_c and RP_c were found in 72% (32/44) and 59% (23/39) respectively of those tumours with a marked degree of elastic tissue within the stroma compared with 67% (37/55) and 36% (17/47) of tumours with moderate elastosis and 49% (36/73) and 26% (18/68)
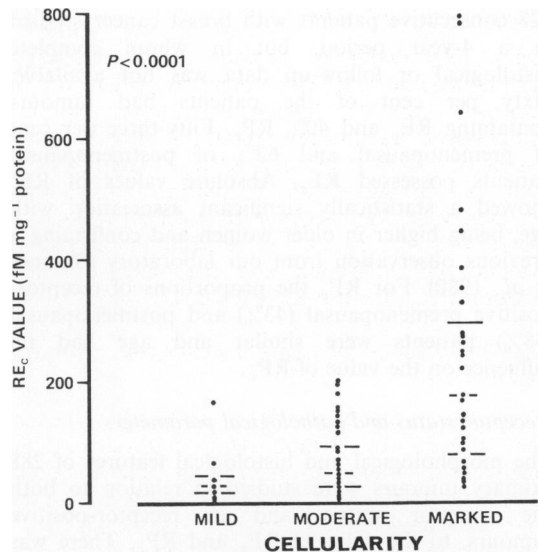
of those with none. For both RE_c and RP_c these were statistically significant associations (RE_c *vs.* elastosis, $P = 0.02$; RP_c *vs.* elastosis, $P = 0.004$) (Figure 3). There was no association between degree of elastosis and value of either RE_c or RP_c ($P = 0.4$).
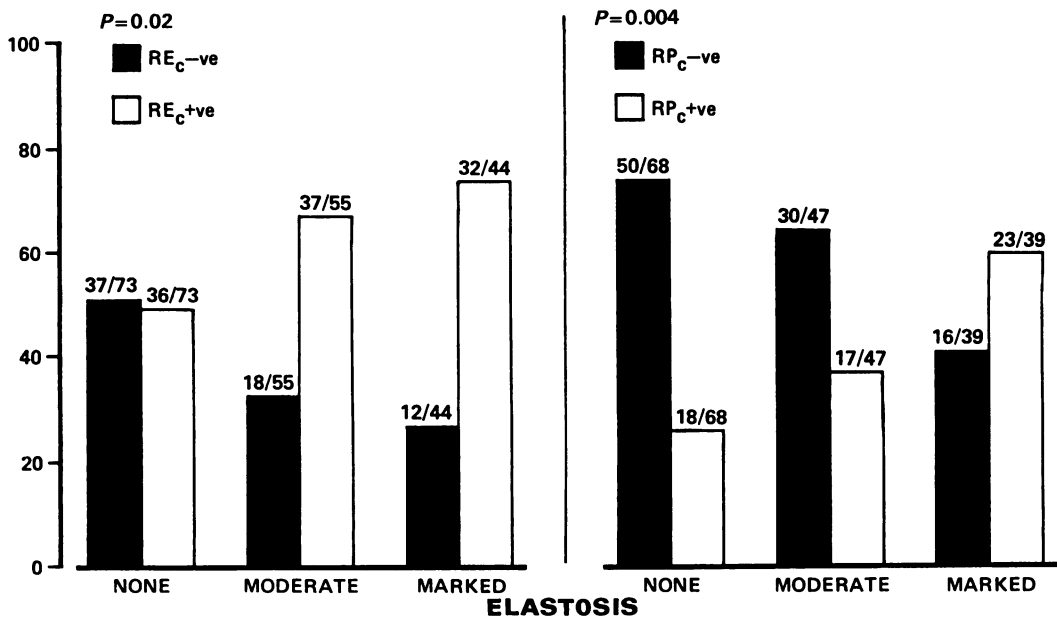

Figure 3 Relationship of RE_c and RP_c to the degree of elastic tissue formation in primary breast cancer.

Lymphocytic infiltration

Only 30% (9/30) of tumours with a marked lymphocytic infiltrate were found to contain RE_c in contrast with 73% (69/94) of tumours with no lymphocytic reaction ($P = 0.0001$). A similar inverse association was found for RP_c. Ninety-three per cent of tumours with a marked lymphocytic reaction were RP_c negative ($P = 0.0004$) (Figure 4). There was no association between the degree of lymphocytic infiltration and the value of either receptor (RE_c, $P = 0.9$; RP_c, $P = 0.3$).

Inter-relationships of grade, lymphocytic infiltration and elastosis

There was a highly significant association between the degree of lymphocytic infiltration and histological grade of infiltrating duct tumours (Table II). High grade tumours contained the most marked lymphoid reaction ($P < 0.0001$). Table III summarizes the inverse association between the degree of elastosis and histological grade, elastosis being most marked in grade 1 tumours ($P = 0.0001$).

Receptor status and node metastases

There was no association between the receptor status of the primary tumour and the number of axillary lymph nodes containing metastases (RE_c vs. nodes, $P = 0.3$; RP_c vs. nodes, $P = 0.7$). The histological findings are summarized in Table IV.

Table II Frequency of concurrence of each degree of lymphocytic infiltration and histological grade in 183 infiltrating duct tumours

| | Lymphocytic infiltration | | |
	None	Moderate	Marked
Grade I ($n = 49$)	34	14	1
Grade II ($n = 94$)	52	29	13
Grade III ($n = 40$)	4	20	16

($P = <0.0001$).

Table III Frequency of concurrence of each degree of elastosis and histological grade in 172 infiltrating duct tumours

| | Elastosis | | |
	None	Present	Marked
Grade I ($n = 48$)	14	12	22
Grade II ($n = 85$)	30	35	20
Grade III ($n = 39$)	25	12	2

($P = 0.0001$).

Receptors and recurrence rates

When the follow-up data were analysed neither age nor menopausal status at the time of first presentation had any influence on the recurrence
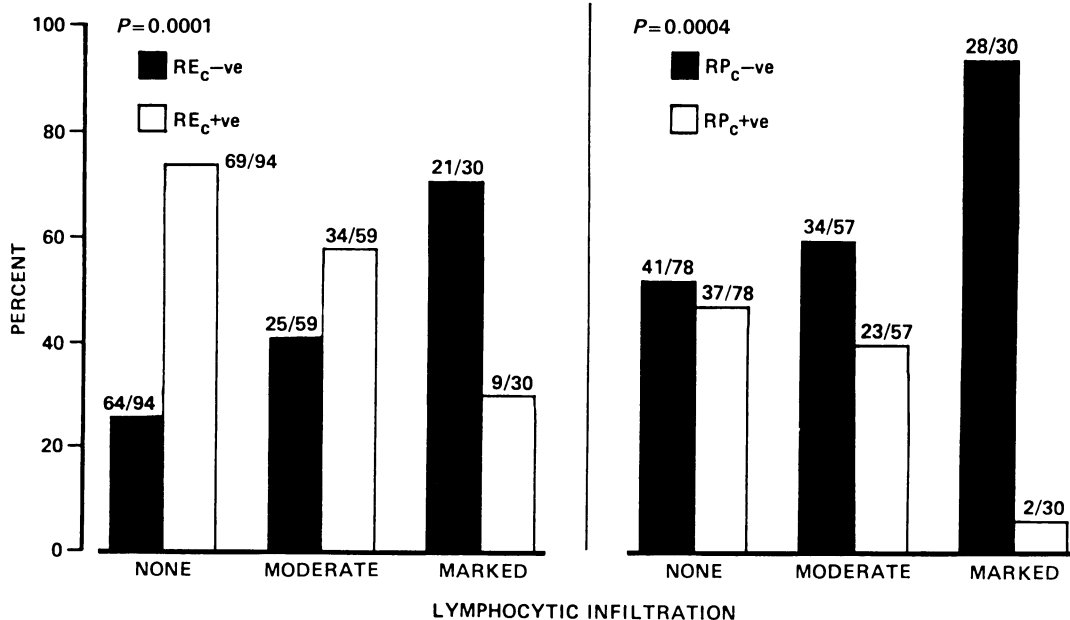

Figure 4 Relationship of RE_c and RP_c to degree of lymphocytic infiltration of primary breast cancers.

Table IV Summary of relationship of RE_c and RP_c receptor status to histological observations

Histological observation	Association with oestrogen receptor (RE_c)	Association with Progesterone receptor (RP_c)
Diameter of primary tumour	None	None
Margin of primary tumour	None	None
Histological type	Statistically none, but all tubular and most lobular tumours RE_c +ve	Statistically none, but all tubular tumours RP_c +ve
Grade of infiltrating duct tumours	RE_c occur most frequently in grade I (well-differentiated) tumours ($P=0.0004$)	RP_c occur most frequently in grade I (well-differentiated) tumours ($P=0.0001$)
Lymphocytic infiltration	Inverse association between lymphoid reaction and presence of RE_c ($P=0.0001$)	Inverse association between lymphoid reaction and presence of RP_c ($P=0.0004$)
Epithelial cellularity:	In RE_c +ve tumours, highest values in most cellular tumours (post-menopausal) ($P<0.001$) but unrelated to receptor status	none
Stromal fibrosis	In RE_c +ve tumours, lowest values in those tumours with marked fibrosis (postmenopausal) ($P<0.0001$) but unrelated to receptor status.	None
Elastosis	RE_c occur most frequently in tumours with elastosis ($P=0.02$)	RP_c occur most frequently in tumours with elastosis ($P=0.004$)
Number of axillary nodes containing tumour	None	None

rate of the tumour. The presence or absence or RE_c and RP_c was analysed with respect to the RFS 15 and 29 months after the last patient entered the study. At a median observation period of 24 months, a statistically significant increase in RFS was found for patients who possessed RE_c compared with those who lacked this receptor ($P=0.02$). This difference was no longer significant at a median period of observation of 34 months (Figure 5). When the patients were divided into 4 groups according to the RE_c content of the tumour (RE_c negative, 5–30, 31–100, >100 fM mg^{-1} cytosol protein) there was no statistical relationship between RFS and the RE_c value at any time (Figure 6). In 163 patients RP_c was also measured. The presence of this receptor was not related to RFS (Figure 7). This was noted in both RE_c positive and RE_c negative tumours, although the number of patients who possessed RP_c and lacked RE_c was very small.

The importance of the presence of metastases in the ipsilateral axillary nodes in determining the prognosis in breast cancer has been emphasised (Say & Donegan, 1974; Fisher *et al.*, 1975). This was confirmed in the present study. The overall recurrence rate was significantly higher in node +ve patients regardless of their receptor status ($P<0.001$). Three years after mastectomy 80% of patients without axillary node involvement

remained free from recurrence compared with 56% of those who had 1–3 involved nodes and less than 30% of patients with 4 or more nodes containing tumour.

RFS was analysed in relation to receptor status and axillary node involvement (Figure 8). There was no statistically significant difference in the RFS between RE_c +ve and RE_c −ve tumours in patients without axillary metastases ($P>0.9$) or in patients with extensive nodal disease (≥ 4) ($P=0.2$). In patients with 1–3 axillary nodes involved, RE_c +ve tumours were associated with a longer RFS than RE_c −ve tumours at a median observation period of 24 months ($P=0.05$), but not at 34 months ($P=0.07$). There were no differences between the RFS of RP_c +ve and RP_c −ve tumours in any axillary node subgroup.

Discussion

Breast cancer varies in its responsiveness to hormones, and is the first disease in which estimation of tissue receptors at the time of initial surgery has been advocated as a method of identifying patients with the greatest risk of recurrence. The purpose of this study was to examine inter-relationships between steroid receptor activity and a variety of histological features, and to
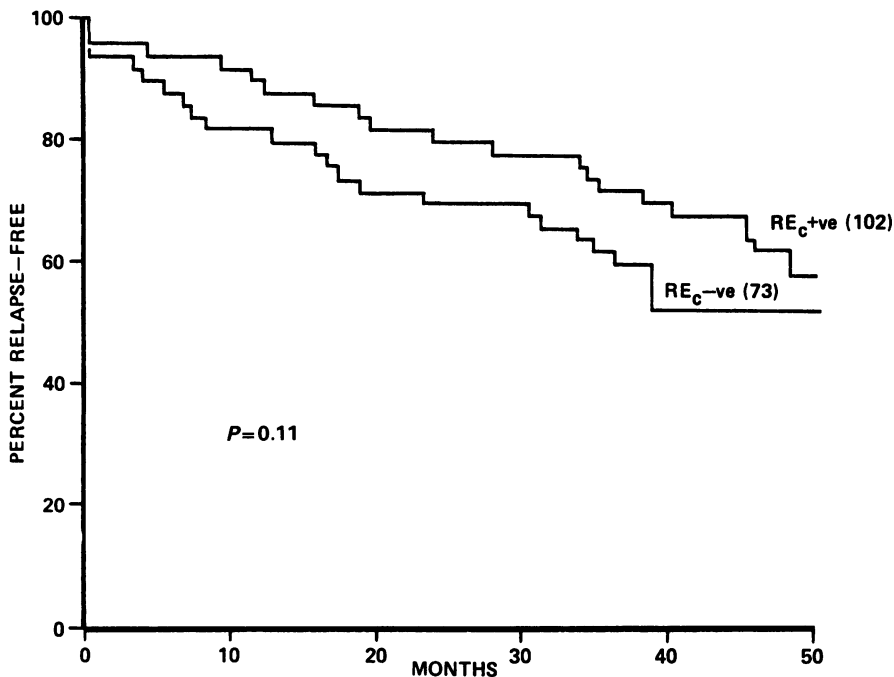
Figure 5   Effect of RE_c status on relapse-free survival.

assess the value of RE_c and RP_c as independent factors in the prognosis of breast cancer.

We have shown RE_c and RP_c to be independent of certain factors known to influence the natural history of the disease, for example tumour size, and the nature of its margin and axillary metastases (Fisher et al., 1975). Although we could not show a statistical relationship between receptors and the histological type it is interesting to note that all tubular carcinomas had both RE_c and RP_c. This confirms the observation of Antoniades & Spector (1979). We also confirmed reports of a high incidence of RE_c in invasive lobular tumours (Rosen et al., 1975; Antoniades & Spector, 1979; Martin et al., 1979b; Rasmussen et al., 1981). Other workers have failed to demonstrate any such association (Johansson et al., 1970; Feherty et al., 1971; Wittliff et al., 1971; LeClercq et al., 1973; Aspegren & Hakansson, 1974), but in most series the majority of tumours were infiltrating duct carcinomas and, as in the present study, the number of uncommon histological types was too small to permit statistical evaluation. The finding that both invasive lobular and tubular carcinomas have a high incidence of RE_c supports the hypothesis that they are extreme variants of the same histological entity (Eusebi et al., 1979).

Although in the past it was generally accepted that there was no association between the presence of RE_c and the histological features of infiltrating duct tumours (Johansson et al., 1970; Feherty et al., 1971; Rosen et al., 1975), only Feherty used the W.H.O. recommended system of grading. More recently, using this method exclusively, Maynard et al. (1978), Martin et al. (1979b), Rasmussen et al. (1981) and Thoresen et al. (1981) have shown a definite relationship between histological grade and RE_c.

Our data agree with the latter reports and in addition have confirmed the findings of Martin et al. (1979b) that the possession of RP_c is also linked to histological grade. Terenius et al. (1974) was unable to show a relationship between the presence or absence of RE_c and grade, but found that RE_c values were statistically higher in well-differentiated tumours. The method of grading was not specified. In the present study, as in that of Heusen et al. (1975) and Thoresen et al. (1981), the mean value of the receptors was similar in all three grades, and thus the significance of the association between grade and presence or absence of receptor is difficult to interpret. Silvestrini et al. (1979) using thymidine-labelling indices have shown that tumours with rapid rates of cell division have a low
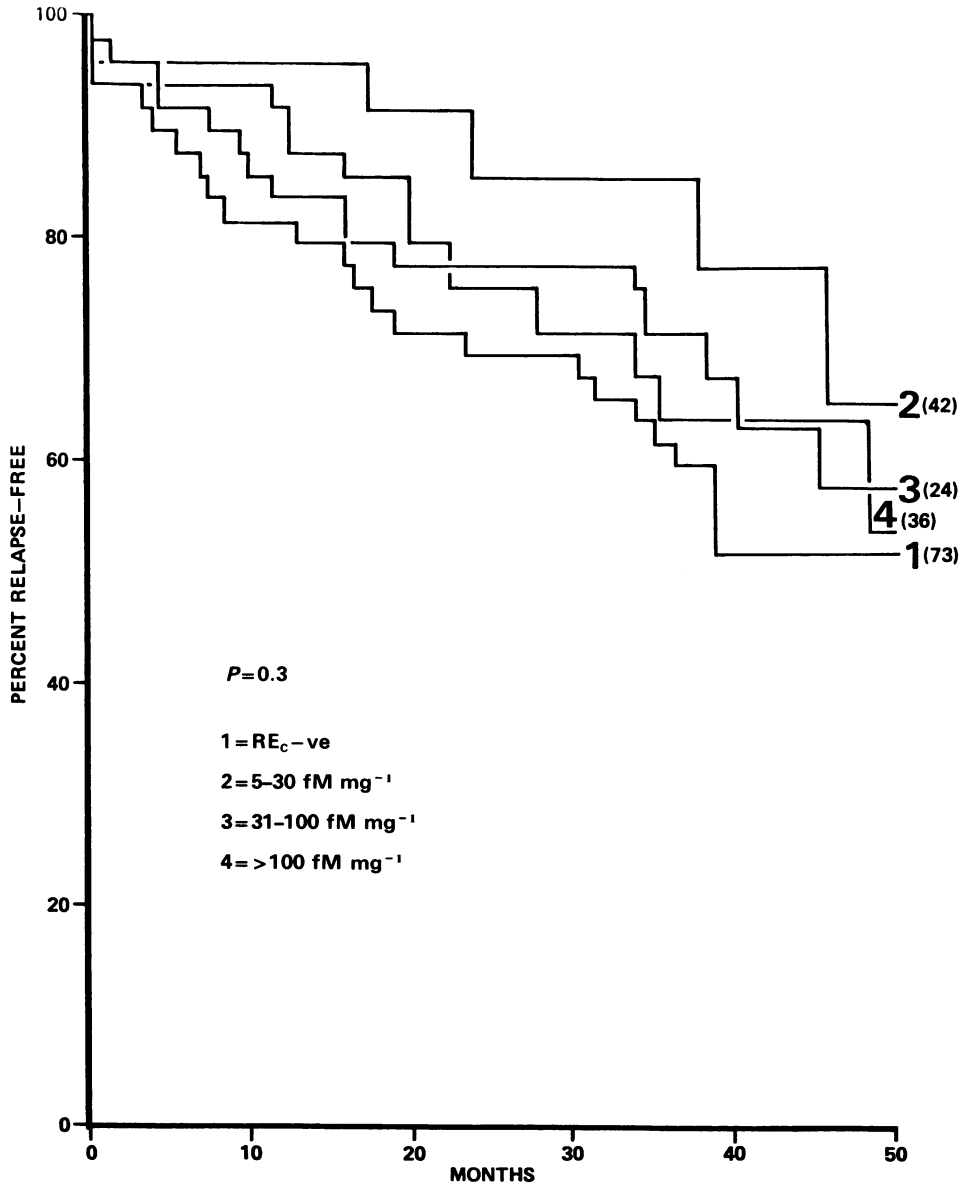
Figure 6   Effect of RE_c value on relapse-free survival.

incidence of RE_c. This, and the frequency with which receptors are found in low grade tumours suggests that receptors are associated in some way with low rates of cellular replication.

Cellularity, when assessed both at the centre and the edge of the tumour to avoid sampling errors, was unrelated to the presence of RE_c and RP_c. However, in receptor-positive tumours, there was a

significant association between the highest values of RE_c and those tumours with the most abundant epithelial component. This was found both in the overall group and post-menopausal patients but not in pre-menopausal patients. Conversely, those tumours with the most marked stromal reaction had the lowest RE_c values. Once again this was not seen in the pre-menopausal patients. By contrast,
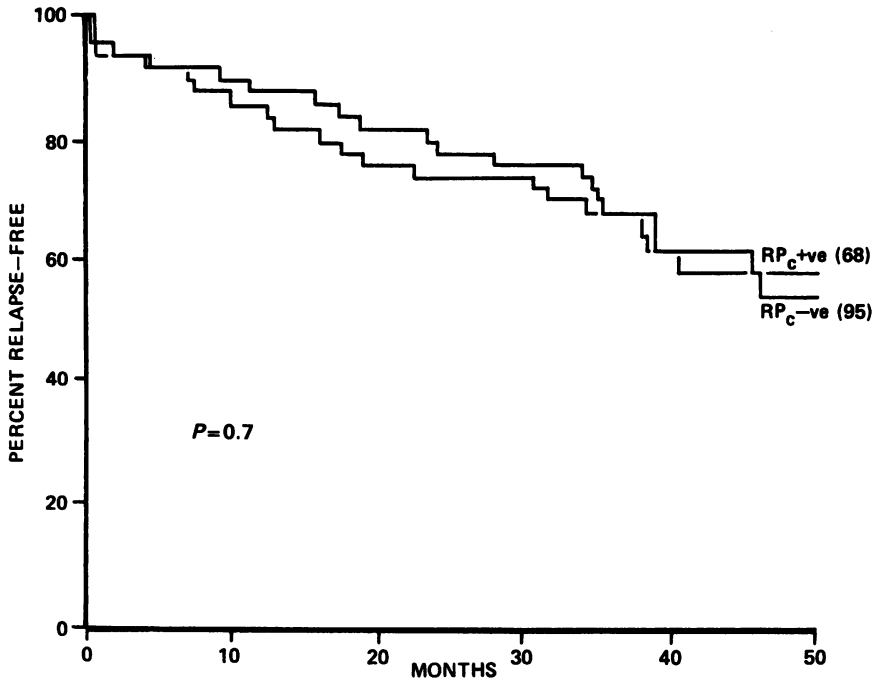
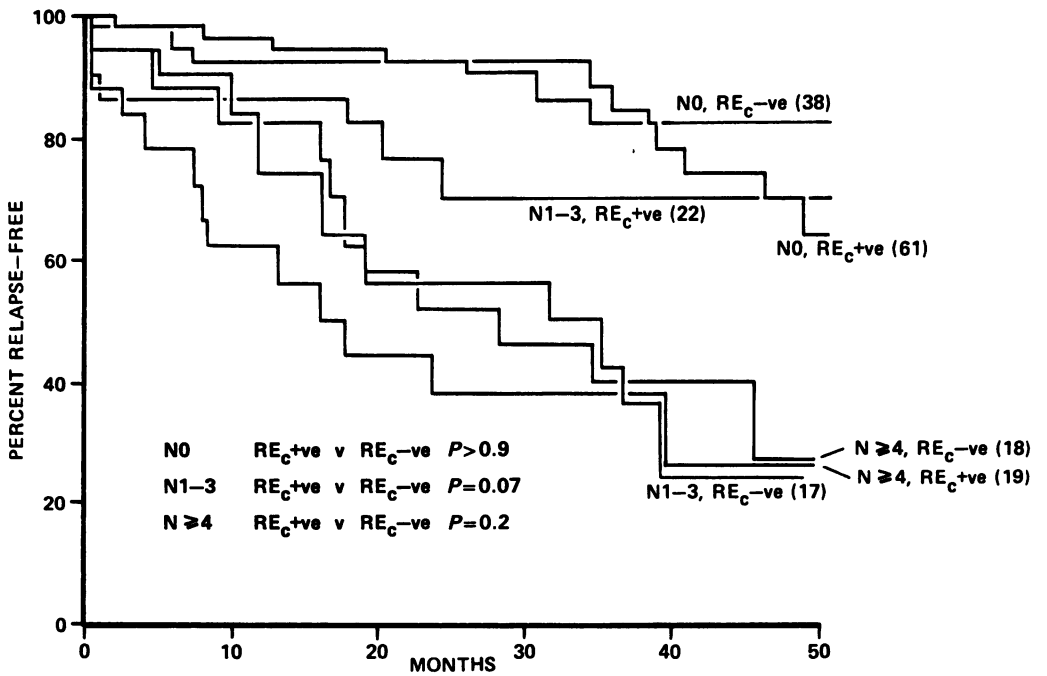**Figure 7**   Effect of RP$_c$ status on relapse-free survival.

Figure 8   Effect of RE$_c$ status and node involvement on relapse-free survival.

the mean value of the progesterone receptors was similar for all degrees of cellularity. These findings are identical with those of Masters *et al.* (1978) and similar, in part, to the results of Terenius *et al.* (1974), Antoniades & Spector (1979) and Martin *et al.* (1979*a*). Rosen *et al.* (1975) observed some association between cellularity and RE_c value but did not consider it significant. Feherty *et al.* (1971) and Rasmussen *et al.* (1981) were unable to show this association. The failure to demonstrate such a link may be the result of unavoidable variation in methods used to assess cellularity (Antoniades & Spector, 1979).

It seems that although cellularity does not affect the frequency with which receptor-positive tumours are identified, it does influence the value of RE_c when present and therefore RE_c negativity, based on a low receptor value, should be considered with caution in tumours of low cellularity for it may only reflect the lack of epithelial cells (Martin *et al.*, 1979*a*). As the presence of RP_c is normally closely linked with RE_c (Martin *et al.*, 1979*b*) the dissociation of RE_c and RP_c in relation to cellularity is unexplained.

There is no readily apparent explanation for the observation that receptors occur infrequently in tumours with a prominent lymphocytic infiltration, a relationship which has been reported previously (Rosen *et al.*, 1975). It seems unlikely that lymphocytes *per se* are responsible for the absence of receptors within a tumour and this inverse association may merely reflect the observed statistically significant association between heavy lymphoid infiltration and poorly differentiated tumours. A lymphoid reaction is known to be closely related to the degree of malignancy (Fisher *et al.*, 1975).

The association of hormone receptors with the presence of elastic tissue within the tumour stroma may have a similar explanation for there was a statistical association between histological grade and elastosis, the latter being most marked in well-differentiated (grade I) tumours. Masters and his colleagues (1976, 1978) and Rasmussen *et al.* (1981) have also found an association between RE_c and elastosis, a feature which occurs frequently in postmenopausal patients, and an association has been reported between RP_c and elastosis (Rolland *et al.*, 1980). They could give no satisfying explanation for their results.

Shivas & Douglas (1972) have shown that patients whose tumours contain elastic tissue survive longer than those who lack it. They are also more likely to respond to endocrine therapy (Masters *et al.*, 1979). Well-differentiated (grade I) tumours have similar properties (McGuire *et al.*, 1977). These reports taken with the present data emphasise that hormone-dependent cells in breast

tumours can be demonstrated both biochemically and histologically and many of the features of breast cancer are interdependent. Steroid receptors cannot be considered in isolation when planning treatment.

The relationship between receptor status and prognosis is not a simple one. Several reports have suggested that early relapse of breast cancer is clearly associated with a lack of RE_c (Maynard *et al.*, 1978; Cooke *et al.*, 1979, 1980; Allegra *et al.*, 1979; Hahnel *et al.*, 1979; Forrest *et al.*, 1980; Westerberg *et al.*, 1980). Patients who have RE_c are reported to live longer than those who lack it (Bishop *et al.*, 1979; Croton *et al.*, 1981). Kinne *et al.* (1981) and Samaan *et al.* (1981) found no overall difference in the RFS of patients with and without RE_c but have found small significant differences in subgroups based on node or menopausal status. The data from the present study, like those of Hilf *et al.* (1980) fails to demonstrate any clear prognostic value for disease recurrence. Similarly there is conflicting evidence that the progesterone receptor is a reliable indicator of prognosis. Pichon *et al.* (1980) demonstrated an increase in RFS for patients with RP_c whereas Allegra *et al.* (1979) and Kinne *et al.* (1981) as in the present study, found no association between the RP_c and RFS.

The reasons for these conflicting results are not clear. Variations in the method of receptor analysis may be important and Forrest *et al.* (1980) showed that by merely moving the "cut-off point" separating receptor-rich (+ve) from receptor-poor (low +ve and −ve) tumours, the prognostic value for RE_c could be eliminated. However, there is good qualitative agreement between centres using the DCC technique, including our own (King *et al.*, 1978), and the present study has employed similar criteria for receptor positivity to previous reports.

Hilf and his colleagues (1980) stressed that clinical factors may cause confusion in interpreting data relating RE_c status to prognosis, and their observations may also apply to RP_c. In early studies numbers were small or receptor data from primary and secondary tumours were combined. In some, no allowance was made for patients receiving additional systemic or local treatment following mastectomy, in others, the status of the axillary nodes was not accurately known, staging being based on pectoral node biopsy, a technique which in our experience may give a false-negative rate of axillary node involvement as high as 20% (Howat & Harris, 1982).

The length of follow-up is short in many of the reports claiming prolonged RFS (Knight *et al.*, 1977; Maynard *et al.*, 1978; Pichon *et al.*, 1980), and actual survival (Bishop *et al.*, 1979; Croton *et al.*, 1981) for receptor +ve patients. Our experience has emphasised the importance of prolonged follow-

up. At a median follow-up of 24 months our results were similar to those of Knight *et al.* (1977), Maynard *et al.* (1978) and Kinne *et al.* (1981). We observed an increase in RFS for RE_c +ve patients with lymph node involvement, but not for any other sub-group. The data suggested that only those with minimal axillary disease (1–3 nodes) benefitted and it was thought that too few node −ve patients had recurred to show any difference attributable to the RE_c status and that patients with extensive nodal involvement (≥ 4) had recurred too rapidly for any beneficial effect of RE_c to become apparent. However, when the median follow-up reached 34 months the difference between RE_c +ve and RE_c −ve patients in the 1–3 node subgroup had disappeared. Hahnel and his colleagues (1979) made similar observations. An apparently advantageous effect of the RE_c in node +ve patients seen in the first 2 years after mastectomy disappeared so that at 5 years they too were unable to demonstrate a significant difference between the RFS of RE_c +ve and −ve patients in any subgroup. Von Maillot *et al.* (1982) obtained similar results for both RE_c +ve and RP_c +ve patients when they were compared with receptor-negative cases. Benson *et al.* (1982) made similar observations on survival. At 5 years

there was no benefit for RE_c +ve patients despite an earlier trend in their favour.

It is not surprising that the progesterone receptor did not influence the RFS in this study for its presence is closely linked to that of RE_c. Thus one might expect that the absence of any effect on RFS of the RE_c would be reflected in the results obtained with RP_c.

As the data obtained in our study did not demonstrate any marked prognostic value for either RE_c or RP_c status and as the presence of these receptors may merely reflect more easily assessed histological features, we conclude that the measurement of these receptors is of no value in identifying those patients at greatest risk of recurrence. Other factors such as tumour size and axillary node status remain pre-eminent as reliable guides to prognosis.

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