CORRELATON BETWEEN OESTROGEN RECEPTORS AND HISTO - PATHOLOGICAL PARAMETERS IN HUMAN BREAST CANCER

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INTRODUCTION

Oestrogen receptors (ER) are cellular proteins which mediate biological responses through high affinity, specific binding with oestradiole in target cells,(Mirecki and Jordan, 1985).

The oestrogen receptors content of human breast cancer has been thought to be a predictor of both prognosis and response to endocrine therapy, (Taylor et al., 1981; Horne et al., 1988 and Raymond and Leong, 1989). The association of oestrogen receptors positivity in the tumour tissue with increased recurrence free survival was reported by Osborne & McGuire, 1979 and Furmanski et al., 1980), Taylor et al., (1981) showed that patients with negative oestrogen receptors in their tumour tissues have a significant decreased disease-free interval.

While useful in predicting endocrine response and providing prognostic information, the quantitative assays for oestrogen receptors are essential in all cases of primary carcinoma of the breast.

Many data so far reported about oestrogen receptors determination have relied on radiolabelled ligand binding assays. Sucrose density gradiant assay and dextran coated charcol radiolabelled binding techniques were the most commonly used, (Hawkins et

al., 1983). These referred only to cytosol receptors (ERc). But, as stimulation of tumour growth by oestrogen requires binding of the hormone to the cytosol receptors (ERc) leading to receptor activation to a form that is translocated to the nucleus where apparent interaction with nuclear receptors (ERn) occurs. Such interaction promotes gene transcription to initiate both protein synthesis and cell proliferation (Mirecki and Jordan, 1985). Therefore, the measurement of ERn becomes equally important as ERc determination.

The more recent technique utilizing monoclonal antibodies specific to oestrogen receptos proteins developed by Magdelanet (1984) and Thorpe et al.,(1984) and that applied in the present study allows a more accurate demonstration of oestrogen receptors at the whole cellular level.

Antoniadis & Spector (1979); Fisher et al., (1981); Roberts & Hahnel (1981) and King et al.,(1985) found that the epithelial cellularity of breast tumours correlates directly with their tendency to be oestrogen receptors positive.However, an exception is found in very poorly cellular indian file type of lobular carcinoma which is usually oestrogen receptors positive inspite of low cell count, (Pich et al., 1977). At the same time.controversy about the relationship between oestrogen receptors content and the tumour grade is existed. While such relationship has been suggested by Heuson et al.,(1975) and Maynard et al., (1978). it was not found by others (Johanssen et al., 1970 and Rosen et al., 1975).

A significant correlation was present between oestrogen receptors content and elastic fibers of the tumour, (Fisher et al., 1981 and Glaubitz et al.,1984). On the other hand, an inverse relationship between oestrogen receptors and fibrosis and necrosis was observed by (Howat et al., 1983).

The present study aims at evaluation of oestrogen receptor status as detected by a monoclonal immunoassay technique and to find the interrelationship between the receptors

positivity and concentration with other histopathological parameters such as histopathological type and grade, nuclear grade, Fibrosis, elastosis and necrosis with correlation with the patient's survival.

MATERIAL AND METHODS

This study included 50 patients diagnosed and histopathologically proved to have operable breast cancers. Specimens from the surgically removed tumours were subjected to oestrogen receptors assay and assessment of different histopathological features. Patients were treated with postoperative radiotherapy and adjuvant hormonal treatment (Nolvadex) for oestrogen receptors positive patients and adjuvant chemotherapy (CMF) for oestrogen receptors negative patients. Follow up was done monthly for a period ranging from 24-30 months especially observing recurrence.

Oestrogen Receptors Assay : Hormone receptors are heat labile protein, so immediately after surgical removal of the specimen, the tissue should be kept at -20 °C to ensure receptors stability, Freshly excised tumour rich tissue specimens 1 cm in diameter were collected from female patients with histopathologically proven breast cancer. The specimens were trimmed from fat and connective tissue, immediately washed in ice cold physiological saline to remove excess blood then placed in a container on ice. Specimens were transported immediately to the laboratory on ice glass mixture and stored frozen at 70 °C for variable periods up to several weeks before assay without decay of receptors. Then the assay was done by using ABBOTT - ER- immunoassay Monoclonal Kit. The results were expressed in femtomoles (fmoles) /mg of cellular proteins, O - 3 fmoles/mg protein was considered as negative ER., >3 - 10 fmoles/mg protein as weakly positive, > 10 - 100 fmoles/mg protein as positive ER., and > 100 - 300 fmoles/mg protein as highly positive ER.

Histopathological Assessment : Formaline fixed specimens from the 50 cases of breast carcinoma were processed as paraffin sections

= moderate(++) and III = marked (+++).

6. **Necrosis :** It is either absent (-) or present (+).

RESULTS

In this study oestrogen receptors were demonstrated in 44 (88 %) out of 50 cases (7 cases were weakly positive, 6 cases were positive and 31 cases were highly positive) as shown in (Table 1).

No statistically significant correlation between histopathological types

(poorly differentiated) tumours showed the lowest oestrogen receptors levels. This correlation was statistically significant (Table 2).

Tumours with marked fibrosis showed less oestrogen receptors concentrations than tumours with mild fibrosis. This inverse relationship was statistically significant (Table 2).

Elastotic tumours were more oestrogen receptors positive than non elastotic tumours. Tumours with marked elastosis showed higher oestrogen receptors concentrations than tumours

and stained with haematoxylin and eosin and Verhoeff 's Van Geson stain to assess the following features :

1. **Histopathological types :** All breast carcinomas included in this study were classified into two fundamental types that is ductal and lobular,(McDivitt et al., 1968).

2. **Histopathological grading :** According to Bloom and Richardson (1957) and Pertschuk et al.,(1985), the following criteria were described and each one marked.

c. Mitotic activity : One point was given for one mitotic figure per high - power field, two points for 2-3 such figures and three points if the number was higher.

The points allocated for each of the 3 criteria were added together ; a total of 3-5 was graded I (well differentiated), 6-7 points graded II (moderately differentiated) and 8-9 points was graded III (poorly differentiated).

with moderate and mild elastosis. This correlation was statistically significant (Table 2).

An increasing levels of oestrogen receptors were observed in tumours with absent necrosis and this correlation was statistically significant (Table 2).

Statistically significant higher 2 year recurrence free survival was found with infiltrating lobular carcinoma, well differentiated histopathological and nuclear grading, few fibrosis and absent necrosis (table 3).

DISCUSSION

The presence of oestrogen receptors in breast carcinoma is now widely accepted as an indicator of potential hormonal responsiveness and the efficacy of endocrine manipulation in the treatment of that tumour, (Furmanski et al.,1980 and Grody et , al., 1982).

The frequency of oestrogen receptors positivity in breast carcinoma varied in different series. Johanssen et al., (1970) reported that only 45%' of cancer breast were oestrogen receptors positive, while 64%' of the reported cases were oestrogen receptors positive in the series of Jakobsen et al., (1984)

In the present study, oestrogen receptors were demonstrated in 44 out of 50 cases of breast carcinoma with incidence rate of 88%. Similar higher rate of incidence of receptors positivity (85 %) were observed by Magdelanet ,(1984). The demonstrated higher frequency might be explained by the method of assay applied in the present study. It is based on the use of monoclonal antibodies recognizing specific antigenic sites on the receptors which are distinct from the ligand binding sites available for measurement by radiolabelled steroid binding techniques, an old method previously used for oestrogen receptors assay., ('king and Greene,1984). Also, the monoclonal antibodies are able to detect receptors whose steroid binding sites are filled with endogenous oestrogen, (De Sombre et al., 1984)- Moreover, monoclonal antibodies are also able to recognize denatured re-

ceptors that would not bind with steroids, as the antigenic binding site is less labile than the steroid binding site (Mirecki and Jordan, 1985).

The incidence of oestrogen receptors in relation to the histopathological type of breast carcinoma was investigated by many authors. Lesser et al., (1981) reported a high incidence of oestrogen receptors positivity in infiltrating ductal than infiltrating lobular carcinoma with a very low incidence in medullary carcinoma. Such results were confirmed by Schwartz et al.,(1985). However, the lobular carcinoma showed an unusually high frequency of oestrogen receptors positive tumours which amounts to 84 % of all the reported cases, (Pich et al., 1977).

In the present study, no statistically significant correlation between histopathological type and oestrogen receptors status was noticed. possibly due to insufficient number of cases. however the 2 year recurrence free survival was significantly higher in infiltrating lobular carcinoma.

The relationship between oestrogen receptors content and histopathological grade is controversial. While Johanssen et al. (1970) and Rosen et al., (1975) denied such relationship, it was reported by Heuson et al., (1975), Maynard et al., (1978) and Mohammed et al., (1986). These authors found that grade I tumours (well differentiated) having the highest oestrogen receptors level and grade III tumours (poorly differentiated) Having the lowest oestrogen receptors levels .

The relationship between oestrogen receptors positivity and histopathological grade had been evaluated in the present study and a statistically significant correlation had been found. Our finding is in agreement with that reported by maynard et al., (1978) and Mohammed et al., (1986) and in contradistinction with that noticed by johanssen et. al., (1970) and Rosen et al., (1975) in this respect, Davis et al., (1986) suggested that endocrine therapy was more effective in patients with well differentiated tumours and chemotherapy was more effective in

patients with poorly differentiated tumours. Moreover there is significantly higher 2 year recurrence free survival in well differentiated tumours in the current study. This was due to the association between grade I tumours and oestrogen receptors positive status as the presence of steroid receptors in grade I tumours is suggested by Mc Carty and Mc Crarty. (1977) to imply a retention of the regulatory control in these neoplasms.

An inverse relationship between fibrosis and both oestrogen receptors content and 2 year recurrenee free survival had been demonstrated in the present study, This relation was statistically signilicant. Cases with mild and moderate degrees of fibrosis contained more oestrogen receptors content than cases with marked degree of fibrosis. This result is similar to that reported by Roberts and Hahnel, (1981) and Howat et al., (1983).

The significance of elastosis in breast carcinoma had been studied by several investigators. Mitchell et al., (1979) And Robertson et al., (1981) found that elastic tissue content and grade have little value in predicting the survival of patients with breast carcinoma. Our results agree with them in the fact that there is no significant effect of elastoais on the recurrence free survival. In contrast, Shivas and Douglas, (1972) and Wallgren et al.,(1976) observed that the degree of elastosis in breast cancers was a significant prognostic indicator and a possible predictor of response to therapeutic hormonal manipulation. These observations were extended by Millis,(1980) who noted an association between the degree of elastosis and the presence of oestrogen receptors as well as response to endocrine therapy. A similar finding was observed by Glaubitz et al.,(1984).

In the present study, in agreement with Millis, (1980) and Glaubitz et al., (1984), elastosis correlated with the presence of oestrogen receptors and there was a trend toward concordance of oestrogen receptors content with those tumours containing more elastic fibres. From this finding we suggest that a combination of elastosis and

oestrogen receptors assessment provides a better predictive index for patients, survival than assessment of elastosis alone which does not significantly affect the recurrence free survival in the present study.

A statistically significant correlation between oestrogen receptors content and absence or presence of necrosis was observed in the present study . An increasing amounts of oestrogen receptors were found in cases with absent necrosis. These findings are similar to that obtained by Fisher et al., (1981) who suggested that necrosis might be a reflection of dedifferentiation. Also we found statistically significant higher 2 years recurrence free survival in cases with absent necrosis.

In conclusion, the findings of the present study demonstrated that oestrogen receptors were present in 88% of cases, oestrogen receptor positivity was significantly correlated with histopathological and nuclear grade, higher elastic content, less fibrosis and absent tumour necrosis. All are features of good differentiated. In addition the recurrence free survival was significantly increased with infiltrating lobular carcinoma, well differentiated tumours, little fibrosis and absent necrosis.

SUMMARY

A monoclonal antibodies immunoassay technique was used to demonstrate oestrogen receptors in 50 freshly excised human breast tumours. 48 cases were infiltrating duct carcinoma and 2 cases were infiltrating lobular carcinoma. the relationship between oestrogen receptors, histopathological type, histopathological and nuclear grades, fibrosis, elastosis and necrosis was evaluated. Oestrogen receptors positivity was demonstrated in 44 out of 50 cases. A significant positive correlation was found between histopathological and nuclear grades and oestrogen receptors content, well differentiated tumours rarely lacked oestrogen receptors. Tumours with marked fibrosis showed less oestrogen receptors tors content than tumours with mild fibrosis, Elastotic tumours were more

oestrogen receptors positive than non elastotic tumours. Those with marked elastosis showed higher oestrogen receptors content than tumours with moderate and mild elastosis. A significant correlation was found between oestrogen receptors content and necrosis, tumours without necrosis showed higher oestrogen receptors content than those with necrosis. The previous results may explain the significant higher 2 year recurrence free survival in cases with well differentiated tumours, little fibrosis and absent necrosis found in the present study.

Table 1 : Estrogen receptor status and concentration in 50 patients with breast cancer .

Oestrogen Receptors (status and Concen tration	NO . of Cases	%
* Negative ER 0 - 3 fmoles/mg protein .	6	12 %
* Weakly positive ER > 3 - 10 fmoles/mg protein .	7	14 %
* Positive ER > 10 - 100 fmoles / mg protein .	6	12 %
* Highly positive ER > 100 - 300 fmoles / mg protein .	31	62

Table (2) : Correlation between histopathological parameters and oestrogen receptors (ER) concentration

Histopathological parameters .	No . of Cases	ER in Fmoles / mg Protein Negative	Weak	Positive	Highly Positive	P - value by One Way Anova Test
Histopathological Type . :						
a - Infilt. duct Carcinoma .	48	6	7	6	29	
b - Infilt . lobular carcinoma .	2	-	-	-	2	P = > 0.05
2 . Histopathological Grade						
I - Welldiff .	27	-	-	-	27	
II - Moderately diff .	18	1	7	6	4	P = < 0.05
III - Poorly diff .	5	5	-	-	-	
3 . Nuclear grade :						
I - Poorly diff .	5	5	-	-	-	
II - Moderately diff .	21	1	8	7	5	P = < 0.05
III - well diff .	24	-	-	-	24	
4 . Fibrosis						
Few +	18	-	-	2	16	
Moderate ++	17	1	1	2	13	P = < 0.05
Dense +++	15	5	6	2	2	
5 . Elastosis						
Absent (-)	4	4	-	-	-	
Mild (+)	10	2	4	4	-	P = <0.05
Moderate (++)	21	-	3	2	16	
Marked (+++)	15	-	-	-	15	
6 . Necrosis :						
Absent (-)	355	-	-	4	31	
Present (+)	15	6	7	2	-	P = < 0.05

Infilt = Infiltrating diff. = differentiated.
P < 0.05 = Significant

Table (3) : Correlation between histopathological parameters and 2 year recurrence free survival (R. F. S .) .

Histopathological parameters .	No . of Cases	2 Year R . F . S . NO .	%	Significance Z test
Histopathological Type . :				
a - Infilt . duct Carcinoma .	48	35	73	z = 4.212
b - Infilt . lobular Carcinoma.	2	2	100	(Sig .)
2 . Histopathological Grade				
I - Well differentiated .	27	23	85	I Versus III
II - Moderately differentiated	18	13	72	Z = 1.96
III - Poorly differentiated .	5	2	40	
3 . Nuclear Grade :				
I - Poorly differentiated .	5	2	40	I Versus III
II - Moderately differentiated .	21	12	57	Z = 1.96
III - well differentiated .	24	21	87.5	(Sig .)
4 . Fibrosis				
Few +	18	16	89	a Versus c
Moderate ++	17	12	71	Z = 1.98
Dense +++	15	9	60	(Sig .)
5 . Elastosis				
Absent (-)	4	2	50	a Versus d
Mild (+)	10	7	70	Z = 1.4
Moderate (++)	21	15	71	(N . S .)
Marked (+++)	15	13	87	
6 . Necrosis :				
a - Absent (-)	355	29	83	Z = 2.09
b - Present (+)	15	8	53	(Sig .)

Infilt . : Infiltrating
Sig . : Significant .
N . S . : Non Significant .

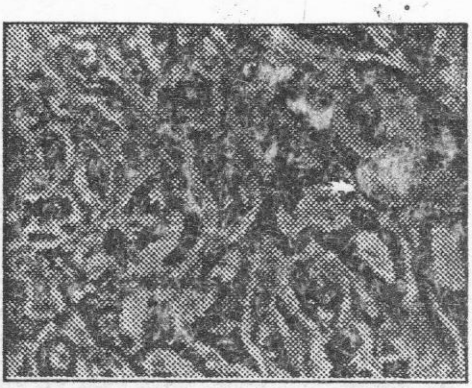

Fig. 1 : Section from breast cancers showing grade I infiltrating duct carcinoma . Note the tubular pattern (Hx . & E.; x 100).

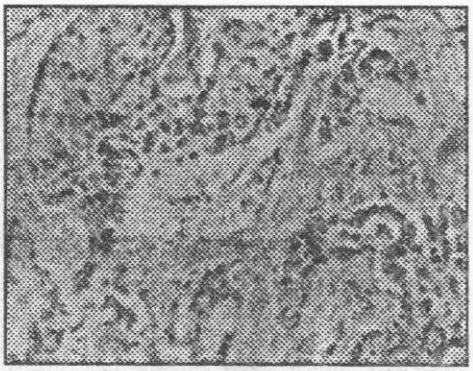

Fig. 3 : Section from infiltrating duct carcinoma showing few fibrosis (Verhoef Van Geison stain X 100).

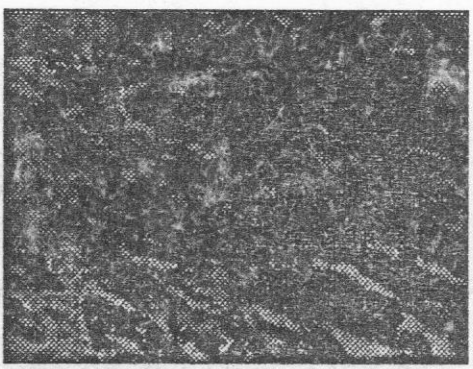

Fig . 2 : Section from breast cancers showing grade II infiltrating duct carcinoma (Hx. & E. X 100) .

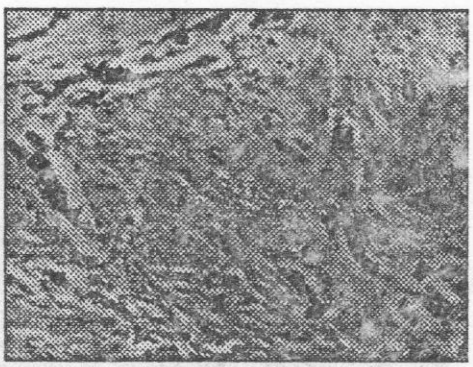

Fig. 4 : Section from infiltrlating duct carcinoma showing moderate fibrosis (Verhoef Van Geison stain X 100).

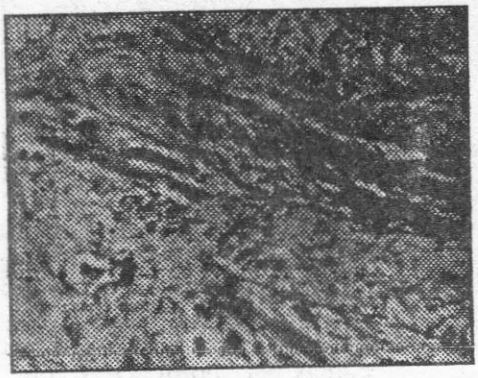

Fig. 5 : Section from an infiltrating duct carcinoma showing dense fibrosis (Verhoef Van Geison, stain X 100).

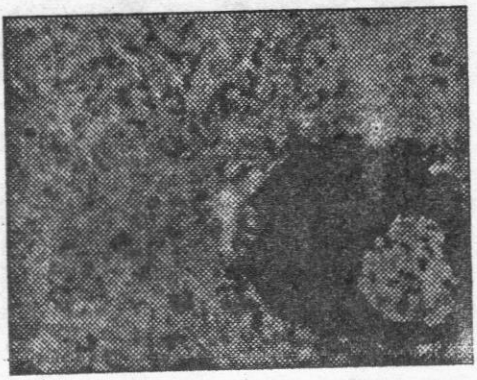

Fig. 7 : Section from an infiltrating duct carcinoma showing marked periductal elastosais (Verhoef Van Geison stain X 100).

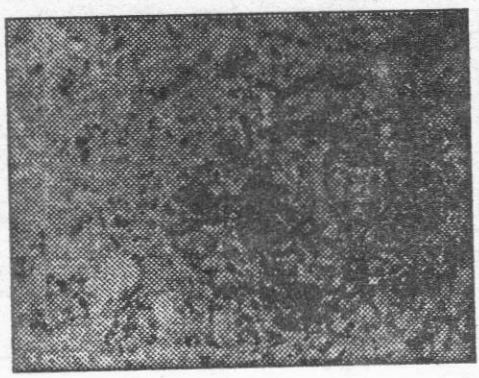

Fig. 6 : Section from an infiltrating duct carcinoma showing mild periductal elastosis (Verhoef Van Geison stain X 100).

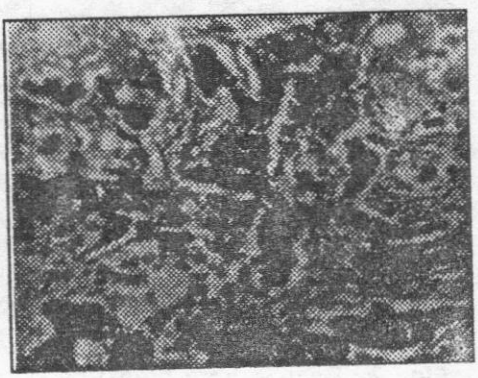

Fig. 8 : Section from an infiltrating duct carcinoma showing an area of necrosis (Hx & E. X 100).

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العلاقة بين مستقبلات هرمون الاستروجين والخصائص الهستوباثولوجيه فى سرطان الثدى .

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ملخص البحث :

شمل البحث خمسون حاله من سرطان الثدى واجريت مقارنه بين مستقبلات الاستروجين وبعض الخصائص الهستوباثولوجيه .

وقد وجد علاقه قويه بين مستقبلات الاستروجين ودرجه السرطان حيث ازداد تركيز هذه المستقبلات فى الحالات ذات الدرجه البسيطه وكذلك ازداد تركيزها مع زيادة كمية الالياف المطاطه .

وقد نقصت مستقبلات الاستروجين مع زيادة كمية الالياف الصلبه وكذلك مع وجود موت موضعى للخلايا . وقد لوحظ ايضا زيادة نسبة الحياة سنتين بدون رجوع الورم مع الحالات ذات الدرجه البسيطه قليلة الالياف الصلبه قليلة الخلايا الميته .

أما كمية الالياف المطاطه فلم يكن لها تأثير مهم على معدل الحياه ومن هذا استنتجنا أن تقييم كمية الالياف المطاطه مع تقييم تركيز مستقبلات الاستروجين فى نفس الوقت ممكن أن يكون له تأثير على معدل الحياه بدون رجوع الورم.