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Oestrogen Receptors in Human Breast Cancer

Problems of Correlation with Histopathological Features

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Summary. Histopathological factors which might explain inconsistency in published data attempting to correlate oestrogen receptor content (ER) and pathological features in primary breast tumours have been investigated in 194 cases. It was found, that unequal assessment of tumour type and of histological grading between observers is one important factor. In terms of grading, however, heterogeneity of growth pattern within the same tumour seems to be of greater significance. No significant correlation was found between histological type of tumour and ER content. However, a trend towards a correlation between the extent of tubule formation (as an indication of differentiation) and ER content was observed.

Key words: Oestrogen receptors – Human breast cancer – Histopathology

In recent years several investigations have attempted to correlate the presence of oestrogen receptors (ER) with histopathological features of breast carcinomas. The reported results, however, have been at variance with each other. In several studies it has been indicated that a high proportion of medullary carcinomas were ER negative (Meyer et al. 1978; Parl et al. 1980; Lesser et al. 1981; Silversward et al. 1980b) and that invasive lobular carcinomas were likely to be correlated with ER positivity (Meyer et al. 1978; Antoniades et al. 1979; McCarty et al. 1980). In several other studies, no relation could be demonstrated between ER and tumour type (Fisher et al. 1980; Heuson et al. 1975; Matsumoto et al. 1978; McGuire et al. 1975; Millis 1980; Terenius et al. 1974 and 1975).

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The relation between ER and the degree of tumour differentiation has also been a matter of controversy. In some studies it has been shown that well differentiated tumours were ER positive more often than anaplastic tumours (Bichel et al. 1981; Elston et al. 1980; Heuson et al. 1975; King 1980; Millis 1980; Parl et al. 1980; Lesser et al. 1981; Silversward et al. 1980; McCarty et al. 1980; Meyer et al. 1978). This, however, has not been confirmed by other studies (McGuire et al. 1975; Matsumoto et al. 1978).

The present investigation was carried out to determine whether any correlation could be found between histological features and ER in Danish women suffering of breast carcinoma, who represent a homogenous ethnic population. Furthermore, it was attempted to gain some insight on factors that might explain the inconsistency of published data on this subject, and to suggest procedures to improve reproducibility and prevent sources of discrepancies.

Materials and Methods

The investigation was based on a series of 194 selected biopsy specimens received for ER determination during the period of 1977–1979 at The Institute of Cancer Research, Aarhus, Denmark. The specimens were obtained from patients with primary breast cancer. The specimens were included in this study according to the following criteria: 1. the biopsy should be representative of the tumour; 2. microscopic sections should be available from both the biopsy actually assayed for ER (section A) as well as from the remaining tumour used for routine histological diagnosis (section B); 3. the cytosol protein concentration should be 3 mg/ml or more in order to avoid false negative receptor results (Poulsen 1981).

Sections A, and 6 months later, sections B, were evaluated by Johan Andersen.

Sections B were reviewed by two pathologists (Luciano Ozzello and Johan Andersen) without knowing either the other pathologist's diagnosis or the result of the ER assay.

The following features were evaluated: 1. Histological type of the tumour according to the new WHO-classification (1982). This classification was chosen because it favors uniformity in recording diagnoses at an international level. 2. The histological grading of invasive ductal carcinomas according to the method described by Bloom and Richardson (1957). This method is based upon an actual scoring from 1 to 3 points (3 representing the most anaplastic variant) of the degree of tubule formation, regularity of the nuclei and number of mitosis (magnification, 400 ×). Scores of these features are added together. Scores of 3–5 indicate well differentiated tumours; 6–7 moderately differentiated tumours and 8 and 9 poorly differentiated tumours.

The ER assay has been described in detail elsewhere (Poulsen 1981).

Results

Table 1 shows that 175 out of 194 cases (90%) were diagnosed equally by both pathologists in terms of histological type. In the remaining 19 cases the types of carcinoma were distributed as follows: pathologist 1/pathologist 2: 7 invasive ductal/4 invasive lobular, 2 tubular and 1 mucinous; 1 invasive ductal with predominant intraductal component/invasive ductal; 1 tubular/invasive ductal; 1 adenoid cystic/invasive ductal; 1 apocrine/invasive ductal, and 8 small cell/8 invasive ductal.

No difference in ER features were observed in equally and unequally assessed tumors and no correlation to type could be found by either pathologist.

Table 1. Oestrogen receptor content in relation to identically and differently assessed tumours by two pathologists

Histological type	No. of cases	ER positive	
		No.	%
Identically assessed			
Intraductal carcinoma	6	0	
Invasive ductal carcinoma	144	84	(58)
Invasive ductal carcinoma with a predominant intraductal component	5	2	
Invasive lobular carcinoma	15	9	(60)
Mucinous carcinoma	4	2	
Papillary carcinoma	1	1	
Differently assessed carcinoma	19	9	(46)

Table 2. Variations in assessment of grading variables in invasive ductal carcinoma

Histological features	No. of tumours[a]	Identical assessment by two pathologists		Identical assessment in 2 samples of each tumour	
		No.	(%)	No.	(%)
Tubule formation	144	129	(90%)	117	(81%)
Mitosis	144	98	(68%)	93	(65%)
Pleomorphism	144	91	(63%)	83	(58%)
Histological grading	144	104	(72%)	96	(67%)

[a] Tumours identically diagnosed as invasive ductal carcinomas by both pathologists

The reproducibility of histological grading of the identically assessed invasive ductal carcinomas was checked by comparing the evaluation given separately by both pathologists according to the criteria described by Bloom and Richardson (1957).

As seen from Table 2, the most reproducible pathological feature was the tubule formation, whereas the evaluation of mitosis and nuclear pleomorphism was reproducible only in two-thirds of the cases. Likewise, the final histological grading was the same for both pathologists in 72% of the cases.

The uniformity of grading within the tumour itself was checked by comparing two different random sections separately by one pathologist (JA). Table 2 shows that the tubule formation also within the tumour was the most constant feature, whereas great variation in nuclear features was observed from one part of the tumour to the other. Therefore only 67% of the tumours would be graded in a reproducible fashion.

Table 3. Relationship between er and tubule formation in identically assessed invasive ductal carcinoma

Tubule formation	No. of cases	ER positive	
		No.	(%)
Identically assessed			
Marked/moderate	34	25	(74%)
Absent	95	53	(56%)
Differently assessed	15	6	(40%)

* $X^2 - 3{,}970$, DF = 1, $p < 0.05$ (marked/moderate vs. absent + unequally assessed)

Considering then the possible relationship between the tubule formation (as the most reproducible variable) and ER content, a trend towards a higher proportion of ER positivity was found in tumours with more prominant tubules (Table 3).

Discussion

In recent years a number of studies have been published on the possible relationship between histopathological features in human breast cancer and ER content. The data have been contradictory. This might be partly due to different biochemical techniques for ER determinations used in these studies and their relative pitfalls (Poulsen 1981).

However, other factors may be of importance, and the present study clearly indicates two of them: 1, the heterogeneity of growth pattern within the same tumour, and 2, the difference of interpretation of the same slides by different pathologists.

For invasive ductal carcinomas, it has been shown in some studies that well differentiated tumours, as judged by the criteria of Bloom and Richardson (1957), or nuclear grading as applied by Fisher et al. (1975) had a significantly higher proportion of ER positive neoplasms compared with more anaplastic ones (Bichel et al. 1981; Elston et al. 1980; Heuson et al. 1975; King 1980; Millis 1980; Parl et al. 1980; Lesser et al. 1981; Silversward et al. 1980; McCarthy et al. 1980; Meyer et al. 1978). However, in other studies this relationship could not be demonstrated (McGuire et al. 1975; Matsumoto et al. 1978).

In this study it was shown that a trend towards a correlation between tubular formation and ER content was apparent suggesting that well-differentiated tumours were more often ER positive. It should be emphasized, however, that if the grading system was used according to Bloom and Richardson (1957) no correlation could be found.

It was shown that variation within any one tumour as well as differences in interpretation of various histological grading features was very pronounced. The assessment of cytological parameters was especially at variance, whereas the evaluation of this invasive growth pattern in terms of tubule formation was better reproducible. Indeed, the variability within the

tumour itself appeared to be of greater significance than the difference in interpretation between pathologists in affecting the final evaluation of the grade of malignancy. Therefore, grading studies performed on a biopsy only may easily lead to confusing results.

It has furthermore been shown in recent studies (Poulsen 1981; Braunsberg 1975; Hawkins et al. 1977; Tilley et al. 1978; Silversward et al. 1980) that breast cancers often contain ER positive and ER negative portions of malignant tumour tissue, and the performance of ER studies on a single biopsy only might easily lead to "false negative" results. This could be another reason why no constant relation between ER content and histological grading features has been obtained.

As to the histological type of tumours, it was shown that there was a good agreement between the two pathologists in 90% of the cases. It is of interest to point out, however, that the investigators failed to agree especially in 3 types of tumours i.e. small cell carcinomas (a tumour which cannot be clearly categorized as ductal or lobular), tubular carcinomas and some invasive lobular carcinomas. Concerning the small cell carcinomas and invasive lobular carcinomas one of the investigators tended not to use the "small cell" terminology, and classified these tumours as either invasive ductal or invasive lobular. As to the tubular carcinoma, the pathologists disagreed in all cases, but it is of interest to note, that tumours typed by one investigator as tubular carcinoma, were typed by the other investigator as highly-differentiated ductal carcinomas (scores 3 points).

In conclusion, the present investigation strongly suggests that variations of histopathological features within the tumours and differences of interpretation by pathologists from different institutions may explain the contradictory results published in the literature about the relationship between ER and histopathology of breast cancers.

Hopefully, immunohistochemical demonstration of ER, especially by means of monoclonal antiestrophilin antibodies, may be helpful in establishing more accurate correlations.

In order to minimize obvious pitfalls in both biochemical ER analysis and histopathology, and in view of the fact that both investigations are of major importance in planning the treatment of women with breast cancer, we suggest that ideally:

1. the surgeon should excise and submit the whole tumour to the pathology laboratory.

2. the pathologist should slice the tumour in thin sections immediately and submit alternate slices for ER analysis and for histological examination in order to avoid "false negative" ER results and to obtain as close a comparison of results as possible;

3. in published reports, different institutions should specify accurately their terminology and the reproducibility of the histopathological criteria applied.

References

Antoniades K, Spector H (1979) Correlation of estrogen receptor level with histology and cytomorphology in human mammary cancer. Am J Clin Pathol 77:497–503

Bichel P, Skovgaard Poulsen H, Andersen J (1981) Estrogen receptor content and ploidy of human mammary carcinoma. Cancer (in press)
Bloom HJG, Richardson WW (1957) Histology grading and prognosis in breast cancer. Br J Cancer 11:359–377
Braunsberg H (1975) Factors influencing estimation of oestrogen receptors in human breast cancer. Eur J Cancer 11:499–507
Elston CW, Blamey RW, Johnson J, Bishop HM, Haybittle JG, Griffiths K (1980) The relationship of ER and histology tumour differentiation with prognosis in human primary breast cancer. Eur J Cancer (Suppl): 59–62
Fisher ER, Gregorio RM, Fisher B (1975) The pathology of invasive breast cancer. Cancer 36:1–85
Fisher ER, Redmond CD, Liu H, Rockette H, Fisher B (1980) Correlation of estrogen receptor and pathological characteristics in invasive breast cancer. Cancer 46: 349–353
Furmanski P, Saunders DE, Brooks SC, Rich MA (1980) The prognostic value of estrogen receptor determinations in patients with primary breast cancer. Cancer 46:2794–2796
Hawkins RA, Hil A, Freedman B, Gore SM, Roberts MM, Forrest APM (1977) Reproducibility of measurements of oestrogen-receptor concentration in breast cancer. Br J Cancer 36:355–361
Heuson JC, Leclercq G, Longeval E, Deboel MC, Mattheim WH, Heimann R (1975) Estrogen receptors. Prognostic significance in breast cancer. In: McGuire PP, Carbone PP, Vollmer EP (eds) Estrogen receptors in human breast cancer. Raven Press New York pp 57–72
King RJB (1980) Analysis of oestradiol and progesterone receptors in early and advanced tumour. Cancer 46:2818–2821
Lesser ML, Rosen PP, Senie RT, Duthie K, Menendez-Botet C (1981) Estrogen and progesterone receptors in breast carcinoma. Correlation epidemiology and pathology. Cancer 48:299–309
McCarty K, Barton TK, Fetter BF, Woodard BH, Mossler JA, Reeves W, Daly J, Wilkinson WE, McCarty KS (1980) Correlation of estrogen and progesterone receptors with histological differentiation in mammary carcinoma. Cancer 46:2851–2858
McGuire WL (1975) Estrogen receptors in breast cancer. In: McGuire WL, Carbone PP, Vollmer EP (eds) Estrogen receptors in human breast cancer. Raven Press New York pp 1–7
Matsumoto K, Sugano H (1978) Human breast cancer and hormone receptors. In: Sharma RK, Criss WE (eds) Endocrine control in neoplasia. Raven Press New York pp 191–208
Meyer JS, Bauer WC, Rao BR (1978) Subpopulation of breast carcinoma defined by S-phase fraction, morphology and estrogen receptor content. Lab Invest 39:225–235
Millis RR (1980) Correlation of hormone receptors with pathological features in human breast cancer. Cancer 46:2869–2871
Parl RP, Wagner RK (1980) The histopathological evaluation of human breast cancers in correlation with estrogen receptor values. Cancer 36:362–367
Poulsen HS (1981) Estrogen receptor assay-limitation of the method. Eur J Cancer 17:495–501
Silversward C, Gustafsson SA, Humla S, Nordenskjold B, Wallgren A, Wrang O (1980a) Estrogen receptor concentration in 269 cases of histologically classified human breast cancers. Cancer 45:2001–2005
Silversward C, Skoog L, Humla S, Gustafsson SA, Nordenskjold B (1980b) Intramural variation of cytoplasmatic and nuclear receptors in human breast carcinoma. Eur J Cancer 16:59–65
Terenius L, Johansson A, Rimsten A, Thoren L (1974) (Malignant and benign) human mammary disease. Estrogen binding in relation to clinical data. Cancer 33:1364–1368
Terenius L, Rimsten A, Thoren L, Lindren A (1975) Estrogen receptors and prognosis in cancer of the breast. In: McGuire WL, Carbone PP, Vollmer EP (eds) Estrogen receptors in human breast cancer. Raven Press New York pp 237–245
The World Health Organization (1982) Histological typing of breast tumors (In press)
Tilley WD, Kneightly DD, Cant ELM (1978) Inter-site variation of oestrogen receptors in human breast cancer. Br J Cancer 38:544–546

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