PREDICTION OF ESTROGEN RECEPTOR STATUS OF INVASIVE DUCTAL CARCINOMA OF BREAST BY HISTOLOGIC GRADE

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ABSTRACT

In human breast cancer, estrogen receptor (ER) status of the tumor has prognostic and therapeutic significance. However, facilities to study ER are not widely available to us. We postulated that if there is a correlation between histologic grade and ER status of invasive ductal carcinoma (IDC), it may help predict the ER status of the tumor. Of 84 cases of breast carcinoma referred to the Cancer Institute of Tehran for immunohistologic study of ER in 1995, 69 cases of IDC that had adequate H & E stained slides were chosen. Using the Nottingham modification of the Bloom-Richardson grading system of IDC, all cases were scored by each of us separately. Conflicting cases were jointly reassessed until a consensus was reached. Sections of paraffin blocks were stained for ER using the avidin-biotin complex method and then they were assessed by a digital image analyzer.

There was an inverse relationship between ER positivity of tumors and each of the grading parameters and the ultimate grade that were all statistically significant ($p<0.0001$). Moreover, further analysis revealed that low histologic grade (with scores of 3 or 4) had a 92.3% positive predictive value (range 62.9%-98.2%) for ER positivity. Similarly, histologic grade—in the presence of score 3 nuclei—had an 83.9% positive predictive value (range 71.2%-91.9%) of ER negativity in tumor cells. These findings suggest that in tumors with histologic grades at both ends of the spectrum, ER status may reliably be predicted in a significant number of cases.

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INTRODUCTION

The estrogen receptor (ER) is an intranuclear protein that binds and mediates the cellular effects of circulating estrogens on cells, including breast carcinoma cells.[1] However, it's presence in breast cancer is quite variable.

The estrogen receptor (ER) status of breast cancer has prognostic and therapeutic significance.[1] Immunohistochemical staining of paraffin-embedded tissue sections is the current method of ER study in clinical practice,[2] but it is not widely available in our country. Of the various histo-logic types of breast cancer, invasive ductal carcinoma (IDC) is the most common type, constituting 65 to 80% of all breast carcinomas.[3] We postulated that if there is a relationship between histologic grade and the ER status of IDC, it may help in predicting the ER status of the tumor whenever the test is not available.

MATERIALS AND METHODS

Between March 1995-March 1996, 84 cases of breast cancer were referred to the Immunohistochemical Section

of the Dept. of Pathology, Tehran Cancer Institute for ER study. 79 of these cases were IDC, and in 69 cases adequate H & E stained slides of tumor were available, which were chosen for further study. Using the Nottingham modification of the Bloom-Richardson grading system (Table I),[4] all cases were independently graded by each of us, blinded to the ER results. Whenever grade scores were not unanimous, slides were jointly reassessed until a consensus was reached.

For ER study, sections of paraffin-embedded tumors were stained with anti-ER antibodies (Dakeopatt, Den-

mark) by the avidin-biotin complex method. Stained slides were then assessed by a Digital Image Analyzer (CAS-200, USA) for percentage of positive cells and intensity of nuclear staining, and subsequent calculation of histoscore (H) as described by McCarty et al.[5] A score of 50 was considered the cut-off point for ER positivity. Statistical analysis included simple chi-square and chi-square for trend-ordered data.

RESULTS

All patients were female, ranging in age from 26 to 79 (mean 47 years; SD 11.5 years). Of these 69 cases, 49 (71%) were ER-positive and 20 (29%) were ER-negative. Histologic grading showed that 29 cases (42.8%) were low grade, 25 cases (36.2%) were intermediate grade, and 15 cases (21.8%) were high grade. Statistical analysis showed a significant inverse relationship between rising scores and ER positivity for each parameter of the grading system, and for the actual grade ($p<0.01$ - $p<0.00001$) (Table II). Moreover, combining all actual and possible scores for any histologic grade in the screening test revealed that a total score of this grading system had a 92.3% predictive value (range 73.4-98.7%) for ER positivity of tumors. Similarly, a total score of 9, when nuclear score is 3, had a 83.9% positive predicitive value (range 71.2-91.9%) for ER negativity of tumors.

There was no significant difference in the percentage of ER-positive tumors between pre- and postmenopausal women (Table III).

Table I. Nottingham modification of the Bloom-Richardson grading system for invasive ductal carcinoma of the breast.

Tubule formation	Score
in >75% of tumor	1
in 10-75% of tumor	2
in <10% of tumor	3
Nuclear pleomorphism	
small, regular, uniform	1
moderate variation in size and shape	2
marked variation in size and shape	3
Mitotic count per 10 hpf	
(field diameter 0.59 mm/area 0.274 mm²)	
0-9	1
10-19	2
>20	3
Total score	
Low grade	3-5
Intermediate grade	6-7
High grade	8-9

Table II. Analysis of histologic parameters and ER results.

	T		N		M		H	
Score	ER+	ER-	ER+	ER-	ER+	ER-	ER+	ER-
1	9	0	11	1	29	4	27	3
2	30	10	36	8	17	7	18	6
3	10	10	2	11	3	9	4·	11
Total	69		69		69		69	

T= tubule formation, N= nuclear pleomorphism, M= mitosis, H= histologic grade
p(T) <0.02, p(N) <0.00001, p(M) <0.0003, p(H) <0.0001.

Table III. Correlation of ER results and menopausal status.

	ER+	ER-	Total
Premenopausal	18 (75%)	6 (25%)	24 (100%)
Postmenopausal	31 (69%)	14 (31%)	45 (100%)

Odds ratio= 0.58 (0.14 - 2.07)
Chi-square= 0.28

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DISCUSSION

The ER status of breast cancer has prognostic and thera-peutic implications. Some types of breast carcinoma such as mucinous and papillary types are generally ER positive.[6] However, IDC is the most common type of this cancer, and is quite heterogenous in regard to ER.

Immunohistochemical staining of fixed, paraffin-embed-ded tissue-sections is now the routine method of studying ER in clinical practice. When stained slides are quantified by image analyzer modalities, results are closly correlated with biochemical measurements of ER and these are more predictive of prognosis.[7]

However, these facilities are not widely available in our country. Previous studies showed that a number of tumor characteristics like nuclear grade, histologic grade, degree of tumor elastosis, and cellularity are related to ER status of tumor cells.[8,9]

The histologic grade of IDC is also an important factor of tumor aggressiveness and prognosis.[10] It has been recom-mended that the histologic grade of IDC be stated in pathol-ogy reports.[11] The modified Bloom-Richardson grading sys-tem is the most widely used system and the one adopted by the World Health Organization.[10]

Our results are in accord with those of Fisher et al.[8] in that a significant inverse correlation exists between histo-logic grade, nuclear grade, and ER positivity of tumor. A score of 1 for any of the grading parameters was strongly associated with positive ER. Further, screening tests revealed that low grade tumors with a total score of 3 or 4 in this grading system could predict ER positivity in 92.3% of cases; similarly, high grade tumors—when their nuclear score was 3—were ER negative in 83.9% of cases. In other words, with histologic grades at both ends of the spectrum of grading, ER status may reliably be predicted. Actually in our patients, all 15 cases with a total score of 3 or 4 were ER positive, and of 11 cases with a total score of 8 or 9 and in the pres-ence of score 3 for nuclei, 9 were ER negative.

Age and menopausal status is another factor that has been found to be related to ER, with more ER positive tumors in the postmenopausal group.[12] However, we could not find such a correlation in our patients; 75% of tumors in pre-menopausal patients and 69% in postmenopausal patients were ER positive.

This discrepancy may well be due to the small number of our cases. These results should of course be corroborated by further large scale studies. Thus, whenever ER study for IDC is not readily available to the pathologist and clinician, histologic grade may supplant it in a small but significant number of cases.

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