Association of Carcinoma Breast: Grade and Estrogen Progesterone Receptor Expression

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ABSTRACT

Objective: To determine the association between histological grade of tumour and estrogen progesterone receptors (ER/PR) expression in unselected invasive carcinoma of breast in Malaysian patients.

Study Design: An observational study.

Place and Duration of Study: Advanced Medical and Dental Institute and Hospital, Kepala Batas, from year 2002 to 2007.

Methodology: Ethical approval from Ministry of Health of Malaysia was obtained. Retrospective case records of patients presented between 2002- 2007 were reviewed for obtaining information on grade of tumour and expression of ER/PR in unselected carcinoma of breast patients. Records with missing data were discarded.

Results: Out of 195 cases evaluated, 42 cases of grade-I tumour were recorded of which 08 (19%) tested positive for ER and 34 (81%) tested negative, 86 cases represented grade-II tumour of which 33 (38%) tested positive for ER and 53 (62%) were negative for ER, while out of 67 grade-III tumours 22 (33%) were positive for ER receptors while 45 (67%) were negative, (χ^2 statistic (df) 4.831, p=0.089). For PR, 192 cases were evaluated and data was missing for 3 cases on PR status. Grade-I tumour consisted of 39 cases of which PR +ve represented 07 (17.94%) and 32 (82.05) cases PR -ve; 86 cases were of grade-II of which 31 (36.04%) were PR +ve and 55 (63.95%) PR –ve. Sixty seven cases of grade-III tumour of which 19 (28.35%) were PR +ve and 48 (71.64) were PR –ve (χ^2 statistic (df): 4.297; p=0.117).

Conclusion: ER/PR positivity trend was highest for grade-II tumours compared to grade-I and grade-III tumours. In general ER positivity was more with grade-II and grade-III tumours compared to grade I tumours. Although results did not reach statistical significance but there was a trend towards ER/PR positivity in grade-II and III tumours. So far, studies from South East Asia reported ER/PR expression more with low grade tumours.

Key words: Estrogen receptor. Progesterone receptor. Histological grade. Invasive breast carcinoma. Prognosis.

INTRODUCTION

Breast cancer is the commonest cancer in Malaysian women. The incidence of breast cancer in Peninsular Malaysia was reported to be lower compared to western countries. The age standardized rate for females was reported to be 47.4/100,000 women.[1] Management of breast carcinoma involves assessment of various tumour related and patient related prognostic factors such as age, performance status, size of tumour, lymph node involvement, estrogen and progesterone receptor (ER/PR), grade of tumour, histological type and HER-2 status to decide on various treatment options. It is well established that ER/PR and HER-2/neu are the most powerful prognostic factors in deciding on treatment.[2]

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So far a limited data has been published on histological grade of tumour correlating with estrogen and progesterone receptor expression. Ayadi *et al.* reported a negative relationship of ER/PR with tumour grade.[3]

Aryandoro *et al.* from Indonesia described that most breast cancer patients have high grade tumours with tumour size more than 2 cm (81.4%) and estrogen positive; low grade tumours were seen to express estrogen receptors than higher grade tumours. A similar situation was seen in Malaysia and Thailand in term of grade of tumour.[4]

As breast cancer in South East Asia has certain features different from the Western countries, the objective of this study was to determine association between the pattern of expression of estrogen and progesterone receptors in relation to grade of tumour at the centre in Penang, Malaysia.

METHODOLOGY

A total of 195 cases of breast cancer were evaluated at Advanced Medical and Dental Institute and Hospital, Kepala Batas, from 2002 to 2007. Study was conducted after ethical approval from the Ministry of Health of Malaysia. This was a retrospective, conducted hospital based study.

All resected specimens of breast carcinoma were routinely analyzed for ER/PR receptors by immuno-histochemistry technique with monoclonal antibodies using antigen-antibody Streptavidin immunoperoxidase technique; other tumour related parameters were reported as per standards. ER and PR positivity was assessed using H-scoring system taking nuclear staining with a score > 50 as positive. Grade of tumour was determined using Bloom Richardson classification of tumour grading on Hematoxylin and Eosin (H&E) stain. Tumours were graded as grade-I to grade-III based on aggressiveness. All the records of cases presenting from year 2002 to 2007 were reviewed retrospectively, for grade of tumour and ER/PR expression in unselected histology. Case records with missing data were discarded.

Data was entered in SPSS version 11.0 and statistical analysis was done. Chi-square test was used to determine the association of ER/PR receptors with grade of tumour. A p-value of < 0.05 was taken as significant.

RESULTS

One hundred and ninety five cases of breast cancer for ER expression and grade of tumour were tested. Overall positivity for ER was 32%, 42 cases of grade-I tumour recorded of which 08 (19%) tested positive for ER and 34 (81%) were tested negative. Eighty six cases represented grade-II tumour of which 33 (38%) were ER positive and 53 (62%) were negative for ER, while out of 67 grade-III tumours, 22 (33%) were positive for ER receptors while 45 (67%) were negative, (χ^2 statistic (df) 4.831 p < 0.089). Results as shown in Table I and II failed to show any association between ER/PR and tumour grade, however, there was a trend of ER/PR positivity for grade-II and grade-III tumours with highest number of tumours showing ER/PR positivity in grade-II tumours.

Table I: Association of ER with tumour grade.

	n	ER Positive frequency (%)	ER Negative frequency (%)	χ^2 statistic (df)	p-value
Grade-I	42	08 (19)	34 (81)	4.831	0.089
Grade-II	86	33 (38)	53 (62)		
Grade-III	67	22 (33)	45 (67)		
Total	195	63 (32%)	132 (68%)		

[a]Chi-square test for independence.

Table II: Association of PR with tumour grade.

	n	PR Positive frequency (%)	PR Negative frequency (%)	χ^2 statistic (df)	p-value
Grade-I	39	07 (17.94)	32 (82.05)	4.297	0.117
Grade-II	86	-	55 (63.95)		
Grade-III	67	31 (36.04)	48 (71.64)		
Total	192	19 (28.35)	-		
		-	135 (70.32)		
		57 (29.68)			

[a]Chi-square test for independence.

One hundred and ninety two cases were available for PR expression and data was missing for 3 cases on PR status. Overall, all positivity for PR was 29.68%. Grade-I tumour consisted of 39 cases of which PR +ve represented 07 (17.94%) and 32 (82.05%) PR -ve, 86 were cases of grade-II recorded of which 31 (36.04%) were PR +ve and 55 (63.95%) PR –ve. Out of the 67 cases of grade-III tumour, 19 (28.35%) were PR +ve and 48 (71.64) PR –ve. (χ^2 statistic (df): 4.297; p=0.117) which failed to show any association between PR and tumour grade.

DISCUSSION

Breast cancer in Asian countries tends to have certain common features such as high tumour size at presentation because of poor screening strategies and high positivity for ER. In Malaysia, the average tumour size at presentation is 5.4 cm in diameter as reported by Hisham *et al.,* and similar findings were reported by Aryandono *et al.* from Indonesia.[4-5]

The finding of high expression of ER in tumours has been reported in several studies from Asian countries.[6-7] Desai *et al.* from India reported lower positivity for ER (32%).[8]

In the present study, the overall positivity for ER was 32% while positivity for PR was 29.68% which is lower than reported from Indonesia by Aryandono *et al.* (ER 52.1% and PR 48.5%), but comparable to Desai *et al.* reported from India.[4,8]

Tumour grade is one of the prognostic factors in breast cancer, tumours expressing higher grade tend to carry poor prognosis.[9] In South East Asian countries most tumours are reported of being high grade including Malaysia.[2,10]

Malik *et al.* reported from Pakistan that amongst breast carcinomas studied, 6% were grade-I, 32% grade-II and 62% grade-III; they also reported a much higher expression of ER (86%) from Pakistan.[11] Similarly, another study from Pakistan by Siddiqui *et al.* showed 11.3% grade-I, 59.2% grade-II and 29.5% grade-III breast carcinomas among sample studied.[12]

So far, a limited data is available on association of ER/PR and histological grade of tumour. Kenneth, *et al.* studied 500 consecutive primary mammary carcinomas at Duke University Medical Centre and cooperating community hospitals in North Carolina.[13] Using a modification of the histologic grading system of the NSABP, they observed a trend towards higher levels of estrogen (ER) and progesterone receptor (PR) content in well (grade-I) and moderately (grade-II) differentiated mammary carcinomas. This relationship between receptor content and histologic grade was enhanced by considering estrogen and progesterone receptor simultaneously. The rank correlation between the

quantitative levels of ER and PR observed by these researchers was 0.74 among histologic grade-I tumours and 0.64 among histologic grade-II tumours. Among the grade-III carcinomas, the majority of tumours displayed either a paucity of measurable receptor or a divergence between levels of estrogen versus progesterone receptor (r=0.19).

Ayadi *et al.* analyzed 155 cases of breast cancer in Tunisian population and inverse relationship between ER expression and tumour grade was reported.[3]

Aryandona *et al.* from Indonesia reported that out of 238 breast cancer patient; among ER positive patients 6 (66.7%) grade-I tumours were ER positive while among grade-II 56 (57.1%) were ER positive, while 54 (48.6) grade-III tumours were ER positive.[4] Again low grade tumours were shown to be expressing estrogen receptors but the number of cases was very small.

As far as association of age with ER expression is concerned most reports in the literature show an association between the expression of ER and age in breast carcinoma while other studies have reported otherwise. The present study did not evaluate this fact.[14,15]

This study did not show statistically significant expression for grade-II tumours but the trend was more for grade-II tumours for ER/PR expression compared to grade-I tumours which may need to be verified in larger sample study. In the present sample size only a very small number of grade I tumours were available. Considering the fact that grade-I tumours are less commonly seen in Asian countries, these results point towards an important fact of conducting a larger sample review in Asian population.

CONCLUSION

In this study, most tumours were ER/PR negative and a trend towards grade-II tumours expressing ER/PR was observed, however, a larger sample size study is needed in Malaysian population to corroborate this finding.

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