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ORIGINAL ARTICLE

Prognostic and predictive factors of invasive ductal breast carcinomas

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Summary

Purpose: *To investigate the significance of certain immunohistochemical markers, namely estrogen (ER) and progesterone receptors (PgR), c-erbB-2 oncogene, p53 tumor suppressor gene and E-cadherin adhesion molecule, in invasive ductal breast carcinomas.*

Methods: *A series of 102 primary breast carcinomas of the ductal type and a standard immunohistochemical technique was used to detect the aforementioned biological markers. The findings were related to various clinical and pathological tumor characteristics, including lymph node metastases.*

Results: *ER and E-cadherin were expressed more commonly in tumors of low histological grade and small number (≤3) of metastatic lymph nodes, whereas c-erbB-2 and the p53 gene were usually expressed in breast tumors of high histological grade and increased number (>3) of metastatic lymph nodes. PgR, on the other hand, was detected frequently in patients with early menarche and metastases in <3 lymph nodes, but this tendency was not statistically significant.*

Conclusion: *The use of these biomarkers, preferably in combination, may provide additional prognostic and therapeutic information which may be proved useful in planning breast cancer treatment.*

Key words: estrogen and progesterone receptors, E-cadherin, c-erbB-2, p53, primary ductal breast carcinoma

Introduction

Breast cancer is the most common cancer in women with over 1 million new cases being diagnosed annually worldwide [1]. The corresponding figure for Europe amounted to 429,900 new cases for the year 2006 [2]. Less common is ductal carcinoma *in situ* which accounts for approximately 3% of symptomatic breast tumors and for approximately 20% of breast malignancies in patients from population-based screening programs [3].

Several clinical and biological characteristics associated with disease-free or overall survival in the absence of adjuvant therapy are used as prognostic factors, whereas a predictive factor is any measurable characteristic associated with a response or lack of a response to a specific treatment. For some types of cancer treatment has become increasingly successful because of the use of biological markers and their contribution in choosing the most appropriate type of therapy.

A number of studies demonstrated the existence of a correlation between the ER and PgR and the various morphological features of primary breast carcinomas [4,5]. These reports, however, yielded contradictory results [6,7].

Sex steroid hormones are considered to be a risk to the genesis and progression of breast cancer [8,9]. In 1896 Beatson was the first to observe an improved clinical outcome in breast cancer patients when he "removed" the endogenous sex steroid hormones [10]. Several decades later Korenman supported this view by proposing "the estrogen window hypothesis" [11].

Meanwhile, the role of ER as a predictor of response to endocrine therapy has been well established with a magnitude that was shown to be proportional to ER levels [12,13]. On the other hand, identification of PgR may be used as a time-dependent prognostic factor [14], the predictive value of which has not been validated yet [13]. Thus, the identification of ER and PgR in human breast cancer cells has been accepted as a tool for both prognosis and prediction of response to therapy and because of these

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they have received considerable attention.

With regard to p53 gene, this has been extensively investigated, particularly in relation to the genesis of inherited breast cancer. There is, indeed, increasing evidence linking the development and progression of breast cancer to the accumulation of mutations at the genomic level [15]. Thus, mutations of p53, such as deletions, are very common in human malignancies, including invasive breast carcinomas [16]. This tumor suppressor gene is involved in the development and progression of breast cancer through the cell cycle by acting as a checkpoint. It has been established that malignant tumors are generally formed when the p53 gene is homozygously deficient. Mutations or overexpression of p53 typically result in conformational or quantitative changes of the corresponding protein, which may be detected by immunohistochemical techniques [17,18].

The c-erb-B2 (HER2-neu) proto-oncogene, which encodes a transmembrane growth factor receptor with tyrosine kinase activity, has become an important area of study for human cancer research. Overexpression of this oncogene leads to cell overgrowth. It has been detected in 9-38% of breast tumors and has been associated with high grade tumors and increased incidence of metastases [19-21]. Tumors overexpressing c-erb-B2 are resistant to endocrine therapy and require blockage of the oncogene in addition to estrogen deprivation [12].

E-cadherin, a calcium-regulated homophilic adhesion molecule, is a subclass of the cadherin family which consists of functionally related transmembrane glycoproteins responsible for the cell-cell adhesion mechanism; it plays a crucial anti-invasive role [4]. Decreased expression of E-cadherin adhesion molecule is associated with high histological grade or dedifferentiation, increased invasiveness of the epithelial cells and development of metastases [22].

The aim of this study was to investigate the presence of any statistically significant association between the above mentioned immunohistochemical markers and the clinicopathological characteristics of breast cancer patients, in order to estimate the possible prognostic or predictive value of these proteins. Moreover, there is always an epidemiological interest for the precise expression of ER, PgR, c-erbB-2, p53, and E-cadherin in ductal breast carcinomas in the female Greek population.

Methods

A series of 102 female patients with infiltrating primary ductal breast carcinomas, with mean age 57.85 ± 13.48 years (range 27-92), was analysed. The clinical and pathological characteristics of the patients studied are illustrated in Table 1. Histological grade was determined according to the criteria of Elston and Ellis [23]. Tumor size, the total number of resected lymph nodes and the number of metastatic lymph nodes were also recorded.

Tissue sections were dewaxed and stained with a standard immunohistochemical technique [24,25]. Endogenous peroxidase activity was blocked with 1% hydrogen peroxide solution dissolved in methanol for 15 min. Pretreatment of the tissue sections took place in a microwave oven at 750 W for 15 min, and this was followed by 10 min incubation with normal rabbit serum (DAKOPATTS Code No. X 902) diluted 1:5 in PBS. The specimens were then incubated overnight at room temperature with the appropriate primary antibodies illustrated in Table 2. Secondary antibody (DAKOPATTS Code No. K 354) incubations lasted 20-30 min. For the identification of c-erbB-2 protein we used the DAKOPATTS Code No. X 901 serum, and the DAKOPATTS Code No. K353 secondary antibody. The incubation lasted 30 min. After staining with 3, 3'-diaminobenzidine tetrahydrochloride (DAB) for 5 min, the sections were counterstained with Harris hematoxylin for one min and, thus, were ready for immunohistochemical evaluation. Prior to each incubation, the tissue sections were washed in PBS solution. The same solution was used to prepare all necessary antibody dilutions. Appropriate positive and negative controls were used.

Statistical analysis

Statistical analysis of the data was performed using the Statistical Package for Social Sciences (SPSS), version 9.0 (SPSS, Inc., Chicago, Il, USA). Continuous

Table 1. Patient histopathological and clinical characteristics

Characteristics	*Number of patients*	*(%)*
Tumor grade		
I	8	7.8
II	63	61.8
III	31	30.4
Tumor size		
T1	29	28.4
T2	61	59.8
T3	12	11.8
Metastases		
Yes	67	65.7
No	35	34.3
Age (years)		
≤45	18	17.6
46-55	27	26.5
>55	57	55.9
Menopause		
Yes	72	70.6
No	30	29.4

Table 2. The primary antibodies and their dilutions used in this study

	Estrogen receptors	*Progesterone receptors*	*p53*	*c-erbB-2*	*E-cadherin*
Primary antibody	Monoclonal 6 F 11	Monoclonal 1 A6	Monoclonal DO-7	Polyclonal	Monoclonal 36 BS
Dilution	1:80	1:60	1:70	1:150	1:50
Manufacturer	Novocastra	Novocastra	Novocastra	DAKO	Novocastra

variables were expressed as mean ± standard deviation and categorical variables were expressed as frequencies and percentages (%). The chi-square test was used to evaluate any potential association between biomarker expression and the biological and histopathological features of the patients. Odds ratios (OR) and 95% confidence intervals (CI) were estimated as the measure of association between biomarker expression and the patient histopathological parameters. Multivariate logistic regression analysis was performed to explore the independent effect of the histopathological parameters on ER expression and survival. All tests were two-tailed and statistical significance was considered for p-values less than 0.05

Results

Body weight

The body weight of postmenopausal women was much higher than that of premenopausal women (74.79 ± 10.14 vs. 66.42 ± 15.10 kg, respectively).

Estrogen receptors

ER were detected as distinct brown nuclear staining in 59 of the 102 cases (57.8%) studied. The association of ER expression with the patients' clinicopathological parameters is shown in Table 3. Patients' age (p=0.018), menopausal status (p=0.033) and the number of metastatic lymph nodes (p=0.016) were significantly associated with the presence of ER (Figure 1). In particular, patients younger than 45 years of age and those older than 55 years were almost 6 (OR=5.9, 95% CI=1.5-23.1, p=0.010) and 3 (OR=2.7, 95% CI=1.1-6.9, p=0.039) times more likely to express ER, respectively, than patients aged 46-55 years. Furthermore, positive expression of ER was almost 3 times more frequent in postmenopausal women compared to premenopausal ones (OR=2.8, 95% CI=1.2-6.8) and more than 4 times more frequent in patients with ≤3 lymph nodes compared to those with >3 lymph nodes (OR=4.3, 95% CI=1.4-12.9). No significant association was found between the expression of ER and age at menarche (p=0.316), histological grade (p=0.262), tumor size (p=0.314) or the presence of nodal metastases (p=0.599). Multivariate logistic regression analysis revealed that <3 lymph nodes (adjusted (a) OR=3.2, 95% CI=1.1-9.7, p=0.012) and postmenopausal status (aOR=2.9, 95% CI=1.3-7.0, p=0.034) remained independently associated with positive expression of ER.

Progesterone receptors

PgR were also localised in the cell nucleus and were identified in 28 out of the 102 cases (27.5%) in the series (Table 4). PgR were not correlated with any of the clinicopathological parameters studied, although many patients experienced an early menarche and had metastases in <3 lymph nodes. There was a tendency toward higher frequency of positive PgR in premenopausal compared to postmenopausal women (OR=2.3, 95% CI=0.9-5.8, p=0.067) and in patients with ≤3 lymph nodes compared to those with >3 lymph nodes (OR=2.9, 95% CI=0.9-9.0, p=0.096). No other association was found between the expression of PgR and any other of the clinicopathological parameters (Table 4).

p53 protein

p53 protein was detected in the nucleus of 31.4% (30/102) breast carcinomas (Figure 2). This expres-

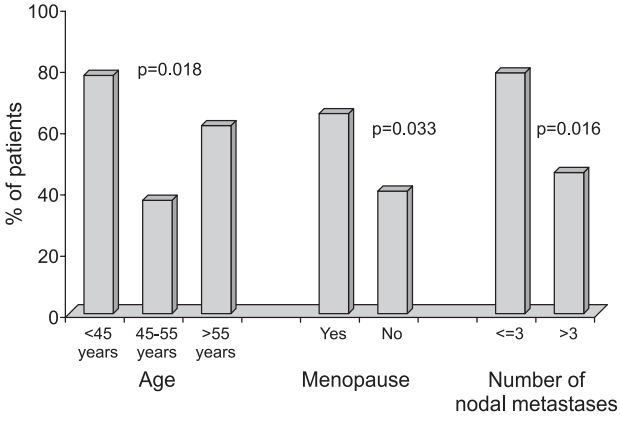

Figure 1. The presence of estrogens receptors in primary breast tumors in association with age, menopause and number of lymph node metastases.

Table 3. Detection of estrogen receptors in primary breast tumors in association with clinicopathological parameters

Parameters	*Estrogen receptors*		*p-value*
	Absence n (%)	*Presence n (%)*	
Age (years)			0.018
≤45	4 (22.2)	14 (77.8)	
46-55	17 (63.0)	10 (37.0)	
>55	22 (38.6)	35 (61.4)	
Menopause			0.033
Yes	25 (34.72)	47 (65.27)	
No	18 (60.0)	12 (40.0)	
Age at menarche (years)			0.316
≤13	14 (43.8)	18 (56.3)	
>13	7 (30.4)	16 (69.6)	
Histological grade			0.262
I	5 (62.5)	5 (62.5)	
II	25 (39.7)	38 (60.3)	
III	15 (48.4)	16 (51.6)	
Tumor size			0.314
T1	15 (51.7)	14 (48.3)	
T2	22 (36.1)	39 (63.9)	
T3	6 (50.0)	6 (50.0)	
Presence of nodal metastases			0.599
Yes	27 (53.6)	40 (59.7)	
No	16 (45.7)	19 (54.3)	
Number of nodal metastases			0.016
≤3 lymph nodes	6 (21.4)	22 (78.6)	
>3 lymph nodes	21 (53.9)	18 (46.1)	

sion was significantly correlated only with the number of nodal metastases (p=0.025); patients with >3 lymph nodes were 5 times as likely to express this protein as patients with ≤3 lymph nodes (OR=5.2, 95% CI=1.3-20.3) (Table 5, Figure 3).

c-erbB-2 protein

The expression of c-erbB-2 protein was membranous and was identified in 31.4% (30/102) breast carcinomas (Figure 4). c-erbB-2 protein expression was significantly associated only with the number of positive lymph nodes (p=0.032); patients with >3 lymph nodes were 5 times as likely to express this protein than patients with ≤3 lymph nodes (OR=4.2, 95% CI=1.1-16.4) (Table 6, Figure 5). Moreover, there was a trend for more frequent positive expression of c-erbB-2 protein in postmenopausal women (OR=2.7, 95% CI=0.8-8.6, p=0.090) and with increasing histological grade (p=0.033 for linear trend).

E-cadherin

E-cadherin adhesion molecule was detected as a membrane-bound protein (with cytoplasmic staining

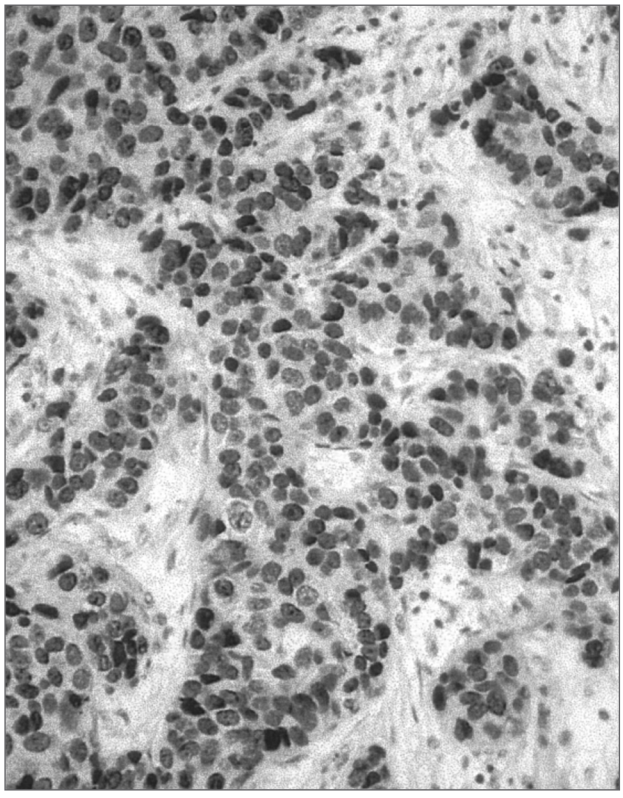

Figure 2. Invasive ductal breast carcinomas immunostained for p53 oncoprotein (×400).

Table 4. Detection of progesterone receptors in primary breast tumors in association with clinicopathological parameters

Parameters	*Progesterone receptors*		*p-value*
	Absence n (%)	*Presence n (%)*	
Age (years)			0.244
≤45	11 (61.1)	7 (38.9)	
46-55	18 (66.7)	9 (33.3)	
>55	45 (78.9)	12 (21.1)	
Menopause			0.067
Yes	56 (77.8)	16 (22.2)	
No	18 (60.0)	12 (40.0)	
Age at menarche (years)			0.355
≤13	23 (71.9)	9 (28.1)	
>13	19 (82.6)	4 (17.4)	
Histological grade			0.772
I	6 (75.0)	2 (25.0)	
II	47 (74.6)	16 (25.4)	
III	21 (67.7)	10 (32.3)	
Tumor size			0.850
T1	22 (75.9)	7 (24.1)	
T2	43 (70.5)	18 (29.5)	
T3	9 (75.0)	3 (25.0)	
Presence of nodal metastases			0.599
Yes	49 (73.1)	18 (26.9)	
No	25 (71.4)	10 (28.6)	
Number of nodal metastases			0.096
≤3 lymph nodes	17 (60.7)	11 (39.3)	
>3 lymph nodes	32 (82.0)	7 (18.0)	

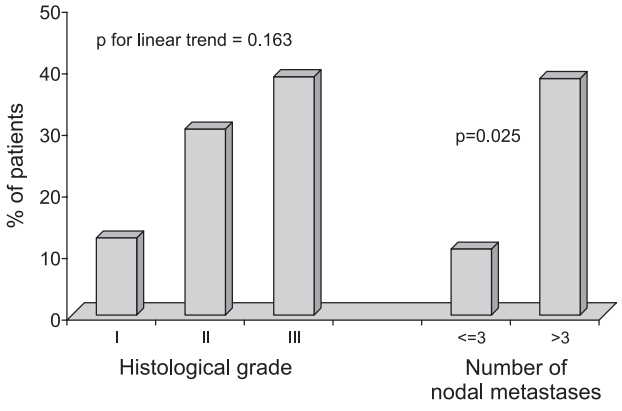

Figure 3. The presence p53 oncosuppressor protein in the primary tumor in association with the histological grade and the number of lymph node metastases.

in a few lesions) in 77 of the 102 cases (75.5%, Figure 6). Table 7 illustrates the frequency of E-cadherin detection in breast cancer cells and its correlation with the clinicopathological parameters measured, which was negligible, with the exception of the number of metastatic lymph nodes. In this regard, there was a tendency toward higher frequency of positive E-cadherin in patients with ≤3 lymph nodes compared to those with >3 lymph nodes (OR=2.8, 95% CI=0.9-8.5, p=0.060).

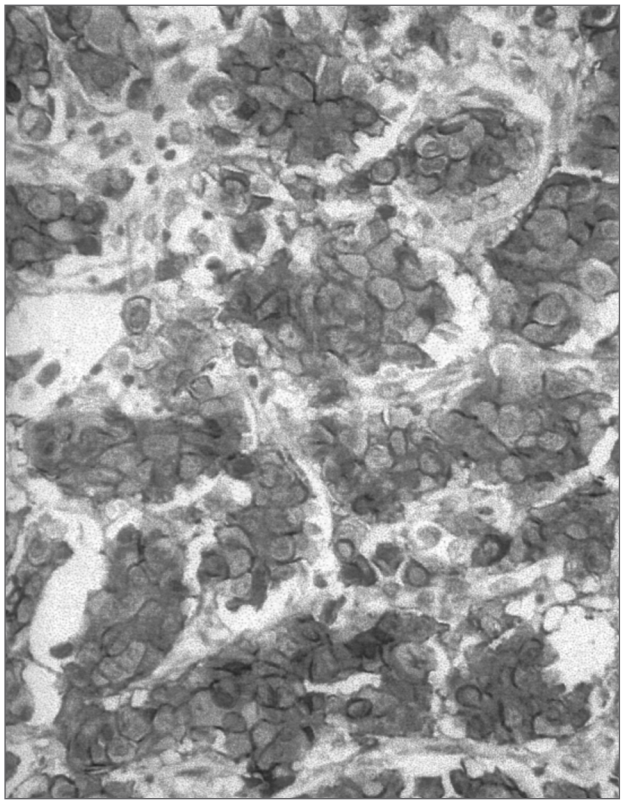

Figure 4. Invasive ductal breast carcinomas immunostained for c-erbB-2 oncoprotein (×400).

Table 5. Detection of p53 in primary breast tumors in association with clinicopathological parameters

Parameters	*p53 oncoprotein*		*p-value*
	Absence n (%)	*Presence n (%)*	
Age (years)			0.931
≤45	12 (66.7)	6 (33.3)	
46-55	18 (66.7)	9 (33.3)	
>55	70 (70.2)	17 (29.8)	
Menopause			0.259
Yes	47 (65.3)	25 (34.7)	
No	23 (76.7)	7 (23.3)	
Age at menarche (years)			0.212
≤13	20 (62.5)	12 (37.5)	
>13	18 (78.3)	5 (21.7)	
Histological grade			0.343
I	7 (87.5)	1 (12.5)	
II	44 (69.8)	19 (30.2)	
III	19 (61.3)	12 (38.7)	
Tumor size			0.867
T1	20 (69.0)	9 (31.0)	
T2	41 (67.2)	20 (32.8)	
T3	9 (75.0)	3 (25.0)	
Presence of nodal metastases			0.175
Yes	49 (73.1)	18 (26.9)	
No	25 (71.4)	10 (28.6)	
Number of nodal metastases			0.025
≤3 lymph nodes	25 (89.3)	3 (10.7)	
>3 lymph nodes	24 (61.6)	15 (38.4)	

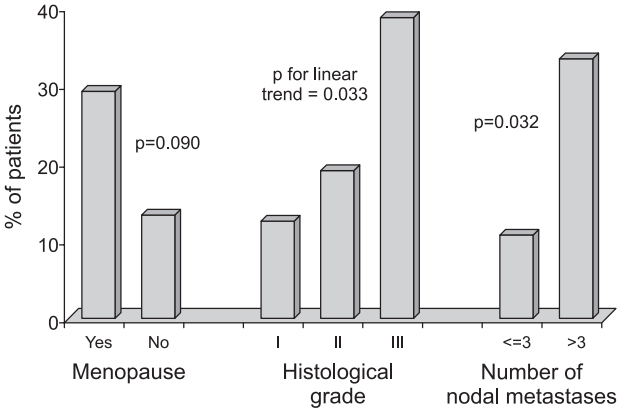

Figure 5. The presence of c-erbB-2 oncoprotein in the primary tumor in association with age, menopause and number of lymph node metastases.

Multivariate immunohistochemical analysis, using ER, PgR, c-erbB-2, p53 and E-cadherin, demonstrated the following correlations: presence of ER and E-cadherin with simultaneous absence of c-erbB-2 and p53 proteins were observed in 62 (47.1%) cases.

Sixty-three cases (61.8%) were positive for ER and negative for p53, whereas in a small percentage (13.7%) both proteins were positive. Further, ER and c-erbB-2 were simultaneously positive in 15.6% of breast carcinomas.

The simultaneous expression of ER and E-cad-

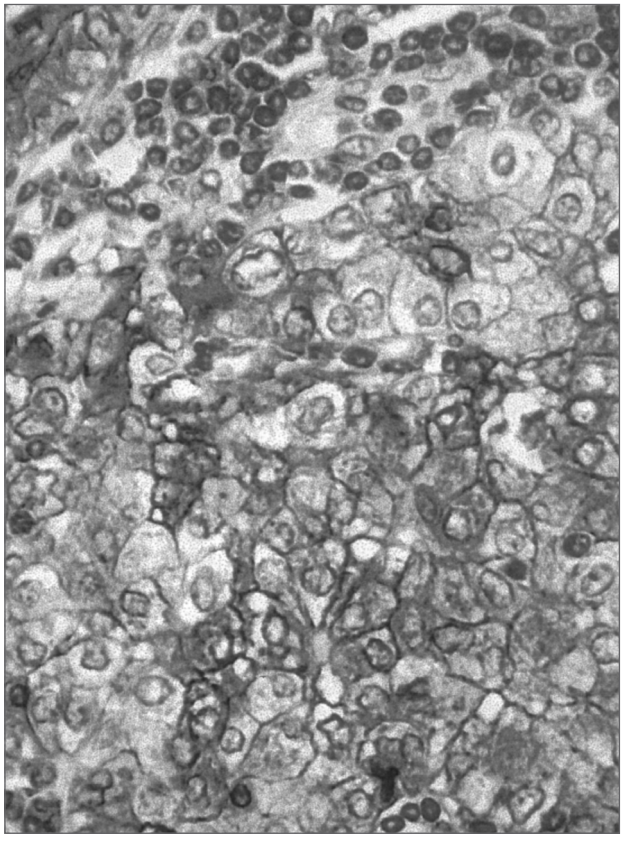

Figure 6. Invasive ductal breast carcinomas immunostained for E-cadherin adhesion molecule (×400).

Table 6. Detection of c-erbB-2 oncoprotein in primary breast tumors in association with clinicopathological parameters

Parameters	*c-erbB-2 oncoprotein*		*p-value*
	Absence n (%)	*Presence n (%)*	
Age (years)			0.237
≤45	16 (88.9)	2 (11.1)	
46-55	18 (66.7)	9 (33.3)	
>55	43 (75.4)	14 (24.6)	
Menopause			0.090
Yes	51 (70.8)	21 (29.2)	
No	26 (86.7)	4 (13.3)	
Age at menarche (years)			0.975
≤13	21 (65.6)	11 (34.4)	
>13	15 (65.2)	8 (34.8)	
Histological grade			0.081
I	7 (87.5)	1 (12.5)	
II	51 (80.9)	12 (19.0)	
III	19 (61.2)	12 (38.7)	
Tumor size			0.489
T1	24 (82.8)	5 (17.2)	
T2	45 (73.8)	16 (26.2)	
T3	8 (66.7)	4 (33.3)	
Presence of nodal metastases			0.838
Yes	51 (76.1)	16 (23.9)	
No	26 (74.3)	9 (25.7)	
Number of nodal metastases			0.032
≤3 lymph nodes	25 (89.3)	3 (10.7)	
>3 lymph nodes	26 (66.6)	13 (33.4)	

herin, along with the simultaneous absence of c-erbB-2 and p53 expression was significantly linked with the number of metastatic lymph nodes (Figure 7) and the tumor's histological grade. More specifically, the findings mentioned above were observed in 60.7% of cases with ≤3 metastatic lymph nodes and in 33.3% with >3 metastatic lymph nodes (OR=3.1, 95% CI=1.1-8.5, p=0.026). The corresponding frequencies for histological grades were 62.5, 33.3 and 16.1% for tumor grade I, II and III, respectively (OR=8.7, 95% CI=1.5-48.5, p=0.007 for grade I, and OR=2.6, 95% CI=0.9-7.7, p=0.080 for grade II, compared to grade III).

Discussion

As it was expected [26,27], the majority of patients (70.6%) in this study were postmenopausal, over 55 years of age, and 58.2% experienced menarche when <13 years of age. This is in accordance with the observations of other authors [28,29] who reported that early menarche and late menopause maximize the number of ovulatory cycles and, therefore, the risk for breast cancer. The effect of endogenous hormones can lead to cell proliferation and the opportunity for accumulation of random genetic errors. Along the same lines, the postmenopausal patients in our series were, on average, 8 kg heavier than the premenopausal ones, and these data are also in agreement with those of other investigators who have reported that overweight postmenopausal women have a higher risk of developing breast cancer [30-32].

The number of metastatic lymph nodes was proportional to the histological grade. The higher the histological grade the higher the number of metastatic lymph nodes [33,34]. Tumor diameter was also proportional to the histological grade and in positive correlation with lymph node metastases, as was also reported by other

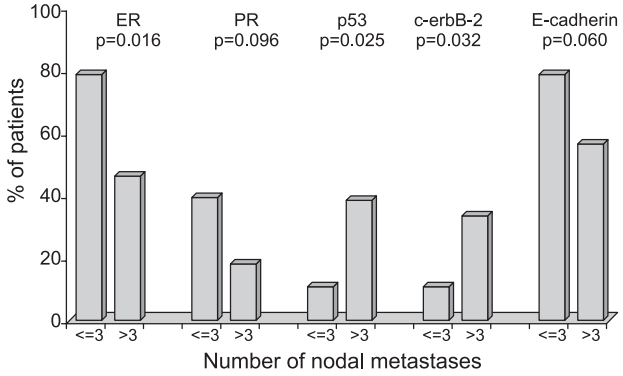

Figure 7. Positive immunoreactivity for the various biomarkers under investigation in primary breast tumors in association with the number of metastatic lymph nodes.

Table 7. Detection of E-cadherin adhesion molecule in the primary breast tumors in association with clinicopathological parameters

Parameters	*E- cadherin adhesion molecule*		*p-value*
	Absence n (%)	*Presence n (%)*	
Age (years)			0.328
≤45	6 (33.3)	12 (66.7)	
46-55	4 (14.8)	23 (85.2)	
>55	15 (26.3)	42 (73.7)	
Menopause			0.858
Yes	18 (25.0)	54 (75.0)	
No	7 (23.3)	23 (76.7)	
Age at menarche (years)			0.495
≤13	3 (9.4)	29 (90.6)	
>13	3 (13.0)	20 (87.0)	
Histological grade			0.977
I	2 (25.0)	6 (75.0)	
II	15 (23.8)	48 (76.2)	
III	8 (25.8)	23 (74.2)	
Tumor size			0.693
T1	6 (20.7)	23 (79.3)	
T2	15 (24.6)	46 (75.4)	
T3	4 (33.3)	8 (66.7)	
Presence of nodal metastases			0.186
Yes	18 (29.0)	44 (71.0)	
No	7 (17.5)	33 (82.5)	
Number of nodal metastases			0.060
≤3 lymph nodes	6 (21.4)	22 (78.6)	
>3 lymph nodes	17 (43.6)	22 (56.4)	

authors [19,35,36]. However, in some studies the association between histological grade or tumor diameter and the incidence of nodal metastases was rather weak [37]. It is apparent that the metastatic potential of tumors differs significantly in different breast malignancies [38,39].

c-erbB-2 protein

According to our immunohistochemical results, c-erbB-2 was expressed mainly in postmenopausal patients having an age at menarche >13 years and tumors with the following characteristics: size >5 cm, histological grade III, and >3 metastatic lymph nodes. c-erbB-2-positive patients had an increased risk of lymph node metastases. More specifically, the possibility of these patients to have >3 metastatic lymph nodes was 4 -fold higher than having <3 metastatic lymph nodes. These results coincide with those of other authors [40-42].

Estrogen receptors

Primary breast tumors expressing ER had a reduced chance of developing lymph node metastases and were inversely proportional to the histological grade, in agreement with recent reports [9,42]. ER-positive expression was independently associated with postmenopausal status [36] and metastases in <3 lymph nodes. In ER-positive patients, the possibility of finding ≤3 lymph nodes was 3-fold higher than finding >3 lymph nodes (Table 3).

Progesterone receptors

There was no statistically significant association between positive PgR and any of the clinicopathological parameters studied. Nevertheless, PgR were mostly identified in patients with age at menarche ≤13 years, and metastases in ≤3 lymph nodes, but this was not statistically significant. Our data, as those of others [12,36], may suggest that PgR is a, more or less, favourable prognostic indicator in breast carcinomas.

p53 protein

In the current study, 31.4% of the tumors exhibited a positive immunoreactivity to p53 protein. Expression of p53 was associated with increased nodal metastases (>3 lymph nodes) and high histological grade. The possibility of nodal metastases in patients with >3 lymph nodes was 3.6-fold higher than in those with

metastases in ≤3 lymph nodes. Positive p53 expression was proportional to the histological grade (grade I = 12.5%, grade II = 30.2%, and grade III = 38.7%). In general, overexpression of p53 was present in high grade tumors, with increased nodal metastases, lack of hormone receptors and, as it has been proffered by other studies, may be associated with poor prognosis [41,43-45]. These patients were most commonly postmenopausal, with an age at menarche ≤13 years [41,46]. The association of p53 expression with the size of the tumor remained questionable [47].

E-cadherin

The E-cadherin adhesion molecule was less frequently expressed in patients with node-positive tumors compared to negative ones. Cadherins are thought to play an important role in activating the mechanism of cancer cell invasion and metastasis [48,49].

The likelihood of having nodal metastases was less common in E-cadherin-positive tumors. Detection of this particular protein in relation to the number of metastatic lymph nodes (≤3 lymph nodes: 71.4%; and >3 lymph nodes: 61.5%) suggests that the absence of E-cadherin is correlated with presence of metastases.

This study demonstrated a weak association between E-cadherin expression and tumor size, while no significant correlation was found with the rest of the clinico-pathological parameters. E-cadherin in itself was not of prognostic value in predicting long-term outcome in women with breast carcinomas [50].

It appears that patients with ductal breast carcinomas expressing E-cadherin in the primary tumors tend to have metastases in <3, if at all, lymph nodes. Such patients are usually premenopausal, having menarche at ≤13 years and tumors of histological grade I and size <2 cm.

Multivariate immunohistochemical analysis

A combinatorial immunohistochemical analysis of our findings indicated that 47.1% of the cases were both ER and E-cadherin-positive and this was correlated with a small number of lymph node metastases (67.9% in ≤3 metastatic lymph nodes; 35.9% in >3 metastatic lymph nodes) and with low histological grade (62.5% grade I, 44.4% grade II and 40.9% grade III).

In 61.8% of the patients ER were positive while p53 and c-erbB-2 proteins were negative, in 13.7% both ER and p53 were positive, while ER and c-erb-B-2 were simultaneously positive in 15.6% of the patients.

Other investigators reported comparable results [51,52]. Such cases with >3 metastatic lymph nodes bore the poorest prognosis.

E-cadherin was also present in cases where both p53 and c-erbB-2 were absent [49,53]. We found that the simultaneous detection of ER and E-cadherin along with the total absence of p53 and c-erbB-2 expression was associated with low histological grade and a reduced lymph node metastatic potential (≤3 metastatic lymph nodes). Such cases may carry a more favorable prognosis.

In agreement with the study of Meijnen et al., the simultaneous detection of c-erbB-2 and p53 proteins was high in primary ductal tumors [52], though considerably more profound in patients with >3 metastatic lymph nodes. Interestingly, markers of well differentiation, such as ER, PgR, and E-cadherin, were higher in patients with metastases in ≤3 lymph nodes.

In conclusion, the current immunohistochemical study (correlated with a spectrum of clinicopathological parameters) has shown that the proteins under consideration can be used as prognostic, and probably predictive markers in infiltrating ductal breast carcinomas. This additional information may be proved indispensable for planning breast cancer treatment.

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