

# Correlation of mammographic appearance and molecular prognostic factors in high-grade breast carcinomas

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## Summary

The aim of our study was to evaluate the association between the mammographic appearance and the biologic characteristics of high-grade breast carcinomas.

Three hundred and twenty patients with breast carcinomas were studied. Histological examination showed 83 (26%) high-grade ductal carcinomas. Immunohistochemistry was carried out by using antibodies against estrogen receptor (ER), progesterone receptor (PR), HER-2/neu, p53 and cathepsin D. In 60/83 high-grade carcinomas we studied the mammographic appearance.

Asymmetric density with poorly defined margins without microcalcifications was the major mammographic finding in 49/60 (~82%) high-grade ductal carcinomas. HER-2/neu positivity (68.7%) and p53 positivity (48.2%) were statistically correlated with asymmetric density with poorly defined margins without microcalcifications in high-grade carcinomas. We observed loss of ER and PR receptors in 50%, whereas loss of PR receptors was observed in 65% of high-grade breast carcinomas. Cathepsin D (>20%) was detected in 38.5% of high-grade carcinomas.

Our findings suggest a significant relationship between mammographic appearance and biologic markers in high-grade breast carcinomas.

**Key words:** Breast carcinoma; Mammographic appearance; Molecular prognostic factors.

## Introduction

Breast carcinoma represents a common disease among Greek women and is considered to be one of the main causes of cancer mortality. These malignant neoplasms form a heterogeneous group of lesions with variable findings and different prognoses.

The clinically available markers such as grading are not sufficient, considering the biological complexity of this clinical entity. Remarkable progress in understanding the molecular foundations of breast carcinogenesis has been made, providing biological factors that can be evaluated easily by means of immunohistochemistry.

In the last decade screening programs have been intensified in Greece, based on eight randomized breast screening trials that suggested a contribution of mammographic screening to breast cancer mortality, although debate continues on this issue.

Several studies comparing screened and symptomatic breast carcinomas have found various associations with regard to estrogen receptor, ER [1], and some have not found any association with regard to progesterone receptor, PR [2].

C-erbB-2 (Her-2/neu) overexpression has strongly correlated with mammographic appearance in non-palpable breast carcinomas [3].

High levels of estrogen-regulated protein cathepsin D, has been associated with poor prognosis [4], whereas in

some studies cathepsin D expression has been associated with screen detected cancers [5].

The aim of our study was to evaluate the association between the mammographic appearance and the biologic characteristics such as ER, PR, c-erbB-2, cathepsin D, p53, a gene that is most commonly altered in human cancer [6], and Ki-67, a cell proliferation marker that labels the G1/S/M/G2 phase [7] of high grade carcinomas.

## Materials and Methods

We studied 320 women with invasive breast carcinomas. The median age of the patients was 55 years (range, 36-76 years).

Histological examination showed 83/320 (26%) high-grade invasive ductal carcinomas.

In 60 out of 83 high-grade carcinomas we studied the mammographic appearance. The standard craniocaudal and lateral views were carried out in all patients. Mammography revealed asymmetric density with poorly defined margins without microcalcifications in 49/60 (~82%). Microcalcifications or a spiculated mass were the major mammographic findings in 11/60 (18.3%).

Immunohistochemistry was carried out by using a panel of monoclonal and polyclonal antibodies against ER (Novocastra), PR (Novocastra), c-erbB-2 /Her-2 neu (Biogenex), cathepsin D (Biogenex), p53 protein (Biogenex), and Ki-67 (Dako).

The chi-square and Fisher's exact tests were used to evaluate the association between mammographically detected asymmetric density with poorly defined margins without microcalcifications and the immunohistochemical profile of each of the molecular factors studied. All statistical tests were two-sided and statistical significance was set at  $p = 0.05$ .

Fig. 1

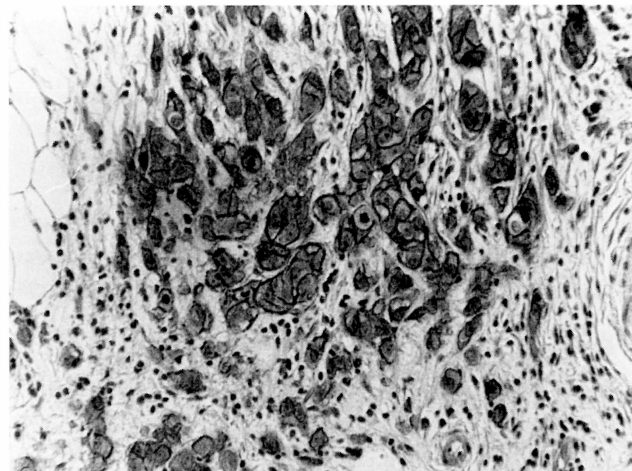
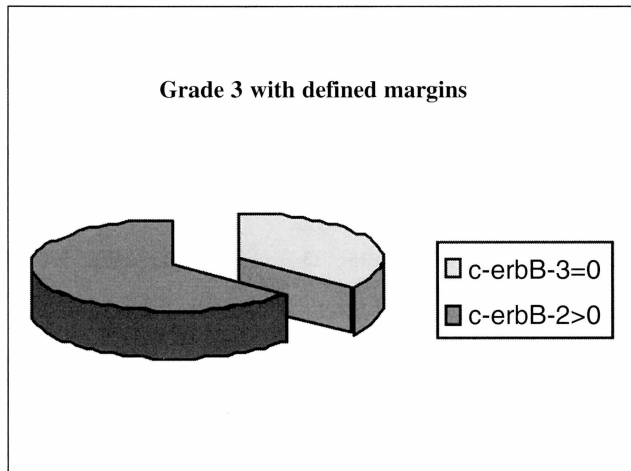


Fig. 2

Fig. 3

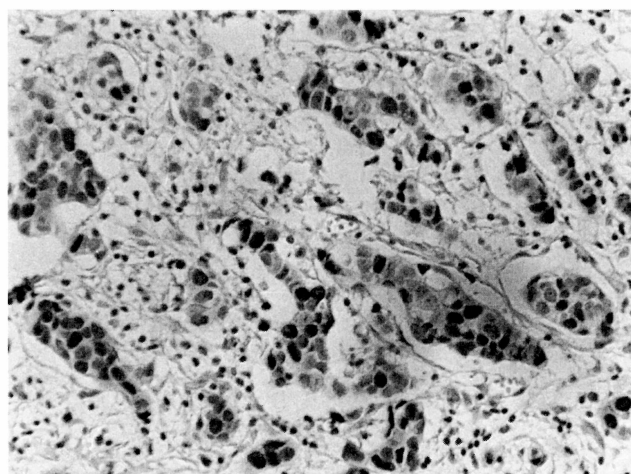


Fig. 4

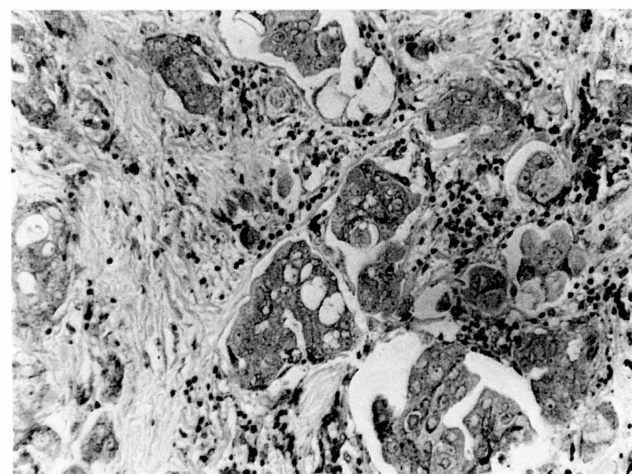


Fig. 5

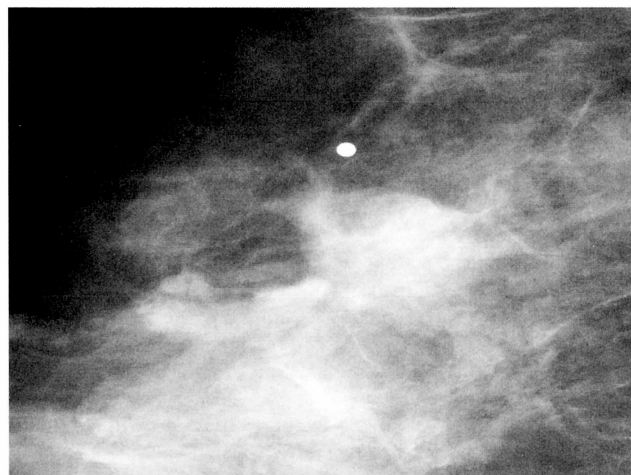


Figure 1. — Presentation mode related to c-erbB-2 expression.

Figure 2. — Membrane positive immunoreaction for c-erbB-2 in a high-grade invasive breast carcinoma.

Figure 3. — Nuclear p53 immunostaining in a high-grade breast carcinoma.

Figure 4. — Granular cytoplasmic cathepsin D immunostaining in a high-grade breast carcinoma.

Figure 5. — High-grade carcinoma with poorly defined margins on mammogram.

**Results**

Forty-one of 83 (~50%) high-grade carcinomas proved to be ER-negative. Fifty-four (65%) of high-grade carcinomas proved to be PR-negative and the prominent mammographic appearance was asymmetric density with poorly defined margins without microcalcifications in 43 (~80%) of them ( $p < 0.05$ ).

C-erbB-2 overexpression was detected in 57/83

(68.7%) high-grade carcinomas. Immunostaining for c-erbB-2 was considered positive when at least 10% of the cells exhibited clear-cut membrane staining.

p53 protein expression and high levels (> 20%) of cathepsin D were detected in 40/83 (48%) and 32/83 (38.5%), respectively.

High mitotic activity (> 10 of malignant cells) was detected in 75/83 (90%) of high-grade carcinomas.

C-erbB-2 (Her-2/neu) positivity was statistically

strongly correlated with asymmetric density with poorly defined margins without microcalcifications ( $p < 0.001$ ). We also found a weaker statistical association between p53 positivity and asymmetric density with poorly defined margins without microcalcifications ( $p < 0.05$ ).

## Discussion

The pressing need for prognostic markers in breast carcinomas arose from the observation that as many as 30% of patients with Stage I breast carcinomas develop recurrence and progression of their disease [8]. Over the past decade, some success in the identification and development of prognostic markers in breast carcinoma has been achieved. Determination of hormone receptor status has proven useful in the identification of breast cancer patients who are at increased risk of developing progression of their tumor [9]. There is a considerable need, therefore, to identify new markers associated with progression and tumor aggressiveness in conjunction with breast imaging studies providing more clues that would help breast specialists make treatment decisions.

In our study, an association was found between progesterone receptor negativity and mammographically detected asymmetric density with poorly defined margins without microcalcifications. Loss of ER and PR in high-grade carcinomas suggests that there is a subsequent decrease of steroid hormones as the aggressiveness of the tumor increases.

Overexpression of Her-2/neu and p53 proteins are the two most common abnormalities in breast cancer and these two biological markers have been thoroughly analyzed as prognostic factors for breast cancer [10]. In our study Her-2/neu overexpression was observed in 68.7% of high-grade carcinomas, whereas p53 protein overexpression was observed in 48% of high-grade carcinomas and correlated mammographically with asymmetric density with poorly defined margins without microcalcifications. More important than the Her-2/neu overexpression prognostic value is its predictive utility, because Her-2/neu overexpression has been associated with altered clinical responsiveness to systemic breast cancer treatment, although the experimental and clinical data are still contradictory [11]. The significant association of Her-2/neu overexpression and mammographically detected asymmetric density with poorly defined margins without microcalcifications ( $p < 0.001$ ) found in our study, could be a combined predictive indicator of lower response rates in future therapeutic interventions and poorer overall prognosis.

The level of expression of protease cathepsin D has been correlated with estrogen receptor status in breast cancer [12]. In our study high levels ( $> 20\%$ ) of cathepsin D were detected in 38.5% of high-grade carcinomas, which is in accordance with recent studies reporting that lack of neoplastic cell cathepsin D expression has been correlated with high nuclear grade breast carcinomas [13].

In conclusion the present data indicate that high-grade invasive ductal carcinomas may display similar mammo-

graphic features to a benign breast mass such as asymmetric density with poorly defined margins without microcalcifications and are correlated with Her-2/neu and p53 overexpression and decreased ER and PR receptors.

## Conclusion

Our findings suggest a significant relationship between mammographic appearance and biologic markers in high-grade breast carcinomas.

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