# Breast Infiltrating Ductal Carcinoma: Analysis of Hormone, HER-2 Receptors and Ki-67 Proliferation Marker

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# Breast Infiltrating Ductal Carcinoma: Analysis of Hormone, HER-2 Receptors and Ki-67 Proliferation Marker

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**A B S T R A C T**

*The aim of this study was to analyse breast carcinomas with discordant receptor status, probably hormonal dependent (estrogen receptor (ER) positive, progesterone receptor (PR) negative or ER-PR+ subgroup profile) infiltrating ductal breast carcinomas not otherwise specified (IDC NOS). Specimens from 90 IDC NOS were grouped into three categories according to hormonal status: dependent (D) (ER+PR+), probably dependent (PD) (ER+PR- or ER-PR+) and non-dependent (ND) (ER-PR-); they were evaluated considering some established prognostic parameters in breast carcinomas. Statistically significant difference was found between tumor receptor status distribution and menopausal status (p= 0.0235), age of the patients (p=0.000467), histological grade (p=0.000003), vascular invasion (p=0.006), HER-2 status (p=0.0039) and Ki-67 proliferation rate (p=0.000311). D tumors were found exclusively in post-menopausal patients (average age 68.9 years), most of which had intermediate (II) grade, without vascular invasion, with HER-2 status score predominantly 0 or 1+ and lower Ki-67 proliferation rate. PD tumors were found predominantly in younger post-menopausal patients (average age 57.5 years), with vascular invasion found in 23% of the cases. ND tumors mostly had higher histological grade, showed the highest percentage of the Ki-67 positive tumor cells and vascular invasion in 30% of the cases. We conclude that the patients with PD breast carcinomas were younger post-menopausal women with the tumors moderately differentiated, HER-2 score 0 or 1+ and with lower Ki-67 proliferation rate.*

***Key words:*** *breast carcinoma, hormone receptors, menopausal status, HER-2, Ki-67*

## Introduction

Since the discovery of the estrogen receptors (ER) in 1960, they have become one of the most important prognostic and predictive markers for breast cancer[1]. The presence of both ER and progesterone receptors (PR) is related to better prognosis and responsiveness to hormonal therapy[2]. Proper understanding of prognostic features of breast cancer can help physicians in the selection of the appropriate treatment for the individual patient. These features are lymph node involvement, tumor size and grade, status of estrogen receptor (ER) and progesterone receptor (PR), status of the biological marker HER2/neu gene expression profile, and patient's age[3]. Thorpe S.M. has argued that all ER-PR+ tumors should be regarded as biologically equivalent to ER+PR+ tumors. However, the response rate to hormonal therapy for ER-PR+ tumors is substantially lower than for ER+ PR+ tumors, suggesting real differences between the two hormone receptor profiles[4–6].

The aim of this study is to reconsider discordant receptor status breast cancers with probably dependent hormonal status (ER+PR- or ER-PR+ subgroup profile) and compare their expression and some established prognostic parameters in breast cancer, i.e. tumor size, lymph node metastases, histological and nuclear grade, menopausal status, age of the patients, Ki-67 proliferation in-

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dex and HER-2 receptor status. The subsets of breast cancer patients that we would seek according to hormonal status are those which are supposed to have less favourable prognosis and higher metastatic potential.

## Materials and methods

### *Study population*

Breast cancer tissue was obtained from surgical specimens submitted to Department of Pathology, University School of Medicine Rijeka, during a two-year period (from September 1st 2002 to August 31st 2004). Among them, 90 cases of IDC NOS were studied. The histology of each case was reviewed and the tumors were classified according to the WHO criteria. Tumors were grouped into three categories according to their hormonal status: dependent (D) (ER+PR+), probably dependent (PD) (ER+PR- or ER-PR+) and non-dependent (ND) (ER-PR-). The age of the patients at the time of surgery was taken into account, and menopausal status was defined clinically according to the regularity of menstrual cycle.

### *Histopathological examination*

After formalin fixation, paraffin embedding and staining with hematoxylin/eosin, histopathological features were determined by pathologist prior to the immunohistochemical examination. Histological grade was assessed using Bloom and Richardson's method, modified by Elson and Ellis[7].

### *Immunohistochemistry*

Three-micrometer sections were mounted on DAKO Chem Mate slides (Code No. S2024), deparaffinised and rehydrated in graded alcohols. Epitope retrieval was carried out on 0.01 M citrate buffer (pH 6.0) in water bath at 97°C for 40 minutes. The slides were then incubated with the primary antibody provided with the Kit, in a DAKO TechMate Horizon automated immunostainer (LJL Biosystems Inc, Sunnyvale, USA). 3,3 diamino-bensidin was used as the chromogen. Substitution of the primary antibody with an isotype matched IgG and omission of the primary antibody served as negative controls.

### *ER and PR receptors*

The samples were stained by anti-receptor antibody; monoclonal mouse antibody, anti-human estrogen receptor a (Clone 1D5, isotype IgG1-kappa, DakoCytomation, Glostrup, Denmark) (dilution 1:50) and monoclonal mouse antibody, anti-human progesterone receptor (Clone PgR 636, isotype IgG1-kappa, DakoCytomation, Glostrup, Denmark) (dilution 1:50). Previously identified strongly staining tumor tissue sections served as positive controls. ER and PR status were expressed in the form of H-score[8], based on a summation of the proportion of tumor cells, showing different degrees of reactivity: negative=0 (0–50), weak=1 (51–100), moderate=2 (101–200), strong=3 (201–300). This gives a maximum total score of 300 if 100% of cells show strong reactivity. In PD group we evaluated weak and moderate positive (ER+PR- or ER-PR+) reactivity of tumor cells (Figure 1a and b).

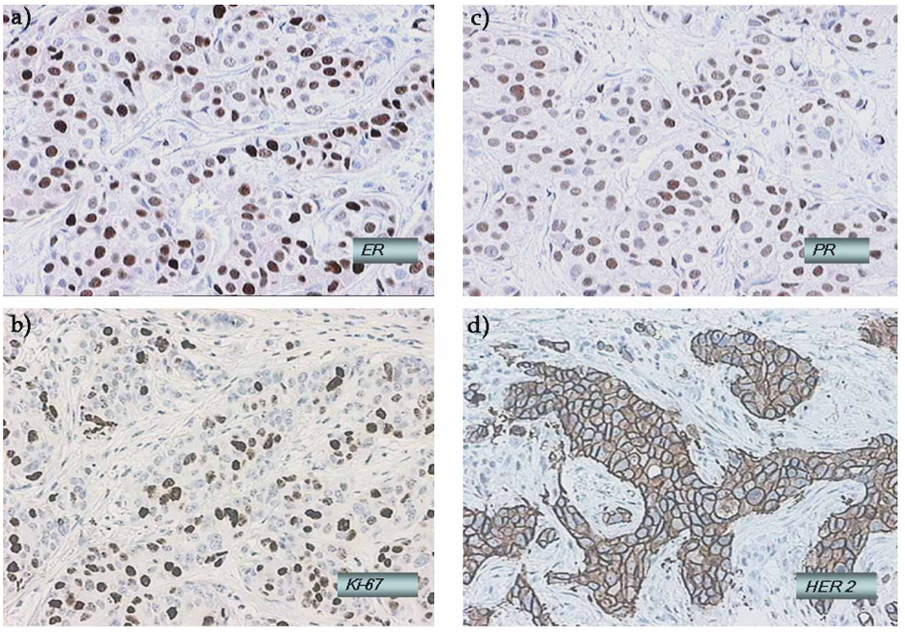


*Fig 1. Invisive duct carcinoma, immunostaining for: a) estrogen receptor (ER), b) progesterone receptor (PR), c) proliferation marker Ki-67, d) HER2/neu receptor.*

**TABLE 1**
CLINICOPATHOLOGICAL BACKGROUND FACTORS FOR IMMUNOHISTOCHEMICALLY DETERMINED HORMONAL STATUS OF 90 BREAST CANCER PATIENTS

| Hormonal status | No. of patients (n=90) | | |
|---|---|---|---|
| | Dependent n=30 | Probably dependent n=30 | Not dependent n=30 |
| Menopausal status | | | |
| Pre-menopausal | 0 | 7 | 5 |
| Post-menopausal | 30 | 23 | 25 |
| Age (years) | 68.9 ± 8.3 | 57.5 ± 13.5 | 59.7 ± 12.1 |
| Tumor size (cm) | 2.22 ± 1.36 | 2.3 ± 2.32 | 3.47 ± 3.54 |
| Type of tumor growth | | | |
| Expansive | 10 | 9 | 10 |
| Infiltrating | 20 | 21 | 20 |
| Histological grade* | | | |
| I | 11 | 7 | 3 |
| II | 19 | 18 | 9 |
| III | 0 | 5 | 18 |
| Peritumoral lymphatic vessel invasion | | | |
| negative | 17 | 14 | 12 |
| positive | 13 | 16 | 18 |
| Intratumoral lymphatic vessel invasion | | | |
| negative | 27 | 27 | 25 |
| positive | 3 | 3 | 5 |
| Vascular invasion | | | |
| negative | 30 | 23 | 21 |
| positive | 0 | 7 | 9 |
| Lymphocyte infiltration | | | |
| negative | 2 | 3 | 2 |
| positive | 28 | 27 | 28 |
| Pathological lymph node status** | | | |
| pN0 | 23 | 22 | 17 |
| pN1 | 1 | 4 | 1 |
| pN2 | 3 | 2 | 7 |
| pN3 | 1 | 2 | 4 |
| pN1mi | 2 | 0 | 1 |
| Expression of HER2*** | | | |
| 0 | 13 | 14 | 10 |
| 1 | 14 | 10 | 5 |
| 2 | 3 | 2 | 3 |
| 3 | 0 | 4 | 12 |
| Ki-67 expression (% of positive cells) | 14.64 | 12.91 | 28.85 |

* I- well diferentiated, II- intermediate, III- poorly diferentiated
** pN – Regional Lymph Nodes, pN0 – No regional lymph node metastasis, pN1 – Metastasis in 1–3 ipsilateral axillary lymph node(s), and/or in internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent, pN2 – Metastasis in 4–9 ipsilateral axillary lymph nodes or in clinically apparent ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis, pN3 – Metastasis in 10 or more ipsilateral axillary lymph nodes; or in infraclavicular lymph nodes; or in clinically apparentipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinnically negative, microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes, pN1mi – Micrometastasis (larger than 0.2 mm, but none larger than 2 mm in greatest dimension)
*** 0 – negative, 1 – weakly positive, 2 – moderately positive, 3 – strongly positive

### *Ki-67 proliferation index*

Staining was obtained by monoclonal mouse antibody, anti Ki-67 (Clone Ki-S5, DAKO, Carpinteria, USA) (dilution 1:50) using the labelled streptavidin biotin (LSAB) visualization system (DAKO Chem Mate Detection Kit, No.5001). Positive staining of chromatin in dividing cells served as internal positive control. Ki-67 proliferation index was expressed as a percentage of positive cells on total of 1000 tumor cells counted. Tumor cells displaying a

nuclear staining were considered positive. Briefly, the sections were deparaffinized with xylene and rehydrated in graded alcohols, followed by the antigen retrieval process (heat-induced epitope retrieval) and primary antibody retrieval, using the microwave and citrate buffer pH 6.1 (Code No. S2031, DakoCytomation). After that, slides were put in the DAKO TechMate Horizon automated immunostainer (LJL Biosystems Inc, Sunnyvale, USA) and the Microwave streptavidin immunoperoxidase (MSIP) protocol was followed. 3,3 diamino-bensidin was used as the chromogen.

*HER-2 receptors*

HER-2 immunostaining was performed using polyclonal prediluted rabbit anti-human HER-2 protein antibody (provided with the HercepTest K5206, DakoCytomation, Glostrup. Denmark). HER-2 status was assessed by a score that includes the intensity and the percentage of positive tumor cells as 0 (negative), 1+, 2+ and 3+ (strongly positive). Only membrane HER-2 immunostaining was considered positive. Previously identified strongly staining tumor tissue sections were used as positive controls.

*Statistics*

Various methods of descriptive and analytic biomedical statistics were used. Pearson X2 and ANOVA were used in comparison analysis of various histopathological features between the three groups (D, PD, ND) and Kendall Tau Correlation test was used for correlation analyses. Statistical differences with p value $< 0.05$ were considered significant. The data was analyzed by SPSS PACKAGE Release 6.0 for PC (SPSS Inc, Chicago, USA).

## Results

The age of the patients at the time of surgery ranged from 30 to 87, with a median age of 63 years. There were 12 pre-menopausal and 78 post-menopausal women in our study population, 62 without lymph node involvement and 28 with lymph node metastasis. Clinicopathological features of tumors were summarized in Table 1.

We found a statistically significant difference between tumor receptor status distribution and menopause ($p=0.024$), age of the patients ($p=0.001$), histological grade ($p=0.001$), vascular invasion ($p=0.006$), HER-2 status ($p=0.004$) and Ki-67 expression ($p=0.001$). D tumors were found exclusively in post-menopausal women, (average age 68.9 years). Most of these tumors had intermediate (II) grade, showed no vascular invasion, HER-2 status score was predominantly 0 or 1+ and Ki-67 proliferation rate was lower. PD and ND tumors were found among both post- and pre-menopausal women with lower average ages (57.5 and 59.7 years, consecutively). The vascular invasion was found at 23% of PD and 30% of ND tumors, while most of the ND tumors had higher histological grade, showed the highest Ki-67 expression (Figure 1c) and HER-2 status score 3+ was found at 40% of these tumors (Figure 1d).

There was no statistically significant difference between tumor receptor status distribution and tumor size ($p=0.11$), lymph node status ($p=0.17$), number of the positive lymph nodes ($p=0.77$), perinodal infiltration ($p=0.43$), findings in peritumoral breast tissue ($p=0.71$), peritumoral ($p=0.43$) and intratumoral ($p=0.66$) lymphatic invasion, lymphocyte infiltration ($p=0.856$) and type of tumor invasion ($p=0.95$). The coefficient of contingency found no statistically significant difference in tumor size among PD, ND and D tumors, although the ND tumors were bigger, had higher percentage (22.4%) of the positive lymph nodes out of totally removed axillary lymph nodes than PD (16.8%) and D (17.4%) tumors. Invasion at the peritumoral and intratumoral lymphatic vessels occurred more frequently. Type of the tumor growth in 70% of the cases was with infiltrating borders.

## Discussion

It is well known that breast cancer depends on various clinicopathological factors, including: metastatic status of the lymph nodes, tumor size, tumor grade, histological grade, HER-2 status and proliferation markers such as Ki 67. We raised the question weather the hormone receptor status of these patients could influence these parameters[9].

Despite the fact that there is a higher absolute age--specific incidence of breast cancer in post- rather than in pre-menopausal women, the dramatic slowing of its increase rate with age suggests a major role of the ovarian activity in its development. As the growth of breast cancer is often regulated by female sex steroids, determinations of the cellular concentrations of ER and PR in the tumor are currently used to predict which patients are of good prognosis and may also benefit from antihormonal therapy[10]. Although more than 60% of human breast cancers are ER-positive, no more than two-thirds of these ER-positive tumors respond to endocrine therapy[11]. It is of interest that both ER and PR appear to be strongly up-regulated in hormone-dependent breast cancer in relation to normal mammary epithelium. It is not clear, yet, what is the exact relationship between ER+ and ER- forms of the disease. Some studies have shown that ER-negative breast cancer cell lines do not transcribe the ER mRNA due to an extensive methylation of the 5'promoter of the gene thus loosing the estrogene receptor expression in human breast cancer cells[12]. The central question in breast cancer research focuses on mechanisms of desensitization of the disease to antihormonal therapy and design of strategies to maintain antihormonal responses in patients. Measurement of PR improves the predictability of hormone dependency of a tumor, but this relationship remains imperfect. Retrospective clinical studies have demonstrated that only 70% of PR-positive and 25–30% of PR-negative tumors respond to hormonal therapy[13]. Still, the ER and PR status at the time of breast carcinoma surgery is used as a

marker of both prognosis and hormone dependency to guide adjuvant therapy[14,15].

The ER positivity is strongly associated with the age at diagnosis, being more prevalent among post-menopausal women[16,17]. In our report, the hormonally dependent patients were exclusively post-menopausal with average age of 68.9 years. According to the last data obtained from Croatian Cancer Registry, the average age of breast cancer patients in Croatia is among 50–69 years. It could be speculated that the increased ER content during menopause might be due to a decreased level of estrogens and the fact that cyclical progesterone secretion in pre-menopausal women limits estrogen stimulation of ER synthesis. A possible explanation of the lower percentage of ER positivity in pre-menopausal patients could be a blockade of ER by endogenous estrogens[14]. It could also be hypothesized that the differences in ER and PR status between pre- and post-menopausal women might be due to a distinct tumor biology and, thus, may truly reflect the differences in its hormone dependency.

It is well known that breast tumors are less well-differentiated among younger women. In an evaluation of breast cancer in women 35 years of age or younger, Rosen et al. found a high incidence of poorly differentiated tumors (53%), and ER-negative carcinomas[18,19]. Our ND patients had the average age of 59.7 years, while PD patients had the average age of 57.5 years. Kollias et al. reported similar findings in an evaluation of 2897 women with breast cancer; higher nuclear grade and lymphovascular invasion observed in women younger than 35 years of age when compared with older women[20].

Our group of ND tumors was predominantly poorly differentiated (60% of them), while in group of D tumors this category was not observed (the tumors were moderately differentiated in 63.33% of cases).The D tumors were mostly of grade II (63.33% of them), and there was no grade III present. Mink et al. showed no correlation between steroid hormone receptor expression and grading, but they showed a slight decrease of ER positive cancers with increasing tumor size[21].

We observed the intratumoral lymphatic invasion in the similar percentage of all three groups of tumors (10–17%). According to our results, the peritumoral lymphatic invasion was slightly higher in ND group, but without statistical significance. Lymphocytes infiltration was also similar in all three groups ($X2=0.3$; $p=0.856$). Vascular invasion was not present in D tumors, while in other two groups it was present in 23% and 30% respectively. The analyzed tumors mostly showed infiltrating borders (in 70% of our cases). Their size was not statistically significantly different in analyzed groups ($F=2.22$; $p=0.11$). It is known that in patients with small tumors treated with adjuvant hormonal therapy the survival was significantly longer[22]. We also found no difference in the changes of the surrounding breast tissue in all three groups.

HER-2 gene amplification or protein over-expression is evident in 20–30% of human breast tumors and correlates with poor prognosis[23,24]. The reason for this association remains unclear, although it has been suggested to rest in increased proliferation, vessel formation and/or invasiveness[25]. In our study, the group of ND tumors had the HER-2 score 3+ in 40% of cases; the fact we didn't observe in D and PD groups of tumors. In this group of tumors there was also a strong correlation between the HER-2 receptors expression and Ki-67 ($p=0.025$). Once again, we observed that the ND tumors showed the highest Ki-67 proliferation rate ($x=28.85\%$, $S=21.58$). So, the poor clinical outcome of these breast cancer patients is expected. Lukashina et al. showed that the higher Ki-67 expression was more frequently associated with positive expression of HER-2/neu. Thus, aneuploid tumors with higher proliferative activity and hyper-expression of HER-2/neu are more aggressive ones and larger in size[26].

The use of Herceptin (the humanized HER-2/neu antibody) has been effective in 20–25% of HER-2/neu positive breast cancer patients, but Witters showed that the pre-menopausal women with HER-2/neu over expression and ER-positive breast tumors would probably receive little benefit, and possibly detrimental effects, from treatment with a HER-2/neu inhibitor alone[27,28].

The status of the axillary lymph nodes is one of the most important prognostic factors in patients with breast cancer. Bader et al. showed that approximately 13% of patients with well or moderately differentiated tumors, less than or equal to 1 cm in size, without lymph or vascular invasion and a low Ki-67 expression had a low risk of axillary lymph node metastases (4.3%)[29]. We observed no statistical difference in the number of positive axillary lymph nodes in three groups that had been investigated ($X2=1.5$; $p=0.17$). It had previously been shown that, if the positive axillary lymph nodes correlated with HER-2 over-expression, the prognosis was poor[24]. According to Collett et al, PR and ER status predicted prognosis in middle age patients (40–60 years) with lymph node positive breast cancer. Analyzing the number of perinodal infiltrations regarding the total number of positive lymph nodes, we found no significant difference among the three tumor groups[30].

In our report, discordant receptor breast carcinomas with PD hormonal status (ER+PR- or ER-PR+ subgroup) were found predominantly in younger post-menopausal women, (approximately 10-years younger than women with D tumors), mostly with intermediate (II) histological grade, HER-2 status 0 or 1+ and lower Ki-67 proliferation rate. Our results of ER+PR- suggest, as previously shown[22], the existence of functionally inactive variants of ER.

We suggest the clinical importance of our results. The patients with D tumors should be primarily candidates for hormonal therapy, especially in old age, while more aggressive PD and especially ND tumors should be treated with proper chemotherapy regimens that should give a possibility of lasting remission.

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## DUKTALNI INVAZIVNI RAK DOJKE: ANALIZA HORMONSKIH, HER-2 RECEPTORA I KI-67 PROLIFERACIJKOG BILJEGA

## SAŽETAK

Cilj ove studije je analiza invazivnog duktalnog karcinoma dojke (tip bez drugih osobitosti-BDO) s različitim statusom receptora, vjerojatno hormonski ovisni (estrogen receptor (ER) pozitivan, progesteron receptor(PR) negativan ili ER-PR+ podgrupa profil). Uzorci od 90 karcinoma su grupirani u tri kategorije prema hormonskom statusu: ovisni (ER+PR+), vjerojatno ovisni (ER+PR- ili ER-PR+) i neovisni (ER-PR-); i evaluirani s obzirom na dokazane prognostičke čimbenike karcinoma dojke. Statistička značajnost je nađena između distribucije tumorskih receptora i menopauzalnog statusa (p=0,0235), starosti pacijentica (p=0,000467), histološkog stupnja (p=0,000003), vaskularne invazije (p=0,006), izražajnost HER-2 statusa (p=0,0039) i Ki-67 proliferacijskog biljega (p=0,000311).Hormonski ovisni tumori su nađeni isključivo kod postmenopauzalnih pacijentica (prosječna dob 68,9 godina), većina ih je bila umjerenog (II) histološkog stupnja, bez vaskularne invazije, sa HER-2 statusom predominantno 0 ili 1+ i niže izražajnost Ki-67 proliferacijskog biljega. Vjerojatno hormonski ovisni tumori su nađeni isključivo u mlađih postmenopauzalnih pacijentica (prosječna dob 57,5 godina), s vaskularnom invazijom u 23 % slučajeva. Hormonski neovisni tumori uglavnom su imali viši histološki stupanj, pokazuju visoki postotak izražajnosti Ki-67 biljega i vaskularnu invaziju u 30% slučajeva. Zaključujemo da pacijentice s vjerojatno hormonski ovisnim karcinomima su mlađe postmenopauzalne žene s umjereno diferenciranim tumorima, koji su s HER-2 statusom 0 ili 1+ i manjim Ki-67 proliferacijskim indeksom.