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EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS IN HUMAN DUCTAL INVASIVE BREAST CARCINOMA NOT OTHERWISE SPECIFIED: IS THERE ANY DIFFERENCE BETWEEN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN?

Joško Petričević[1], Marija Petković[2] and Nives Jonjić[3]

[1]School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina; [2]University Department of Oncology, Rijeka University Hospital Center; [3]Department of Pathology, School of Medicine, University of Rijeka, Rijeka, Croatia

SUMMARY – Determination of hormone receptors is of utmost importance in planning therapy in patients with breast cancer. The aim of the study was to assess the expression of estrogen (ER) and progesterone (PR) receptors in ductal invasive breast carcinoma not otherwise specified (NOS) according to patient menopausal state and tumor histopathology. The study included 549 patients treated at University Department of Surgery, Rijeka University Hospital Center, between January 1, 2000 and January 1, 2005. The patients were diagnosed with breast cancer and underwent mastectomy. ER and PR status was determined by immunohistochemistry. Study results showed no statistically significant differences in the expression of ER and PR, tumor size and grade of histologic differentiation between premenopausal and postmenopausal women. However, tumor size and grade of histologic differentiation differed significantly according to the expression of hormone receptors. Tumors greater than 5 cm in size were mostly ER- in premenopausal (P=0.012) and PR- in postmenopausal (P=0.044) patients. Poorly differentiated cancers were associated with ER-PR- status in both premenopausal and postmenopausal patients (P<0.001). Hormone dependent tumors (ER+PR+) were of smaller diameter and lower histologic grade, while hormone independent tumors (ER-PR-) had greater diameter and higher histologic grade, the difference being statistically significant (P=0.004 and P<0.001, respectively). Study results on the characteristics of ductal invasive carcinoma according to hormone status were consistent with those described in the literature. Considering controversies about the role of steroid receptors in endocrine therapy response, our future objective is assessment of the 5-year prognosis in our patients.

Key words: *Carcinoma, ductal, breast; Premenopause; Postmenopause; Receptors, estrogen; Receptors, progesterone*

Introduction

Breast cancer is the most common malignant tumor in women, accounting for 20% of deaths in female population, thus posing a major socioeconomic and health problem in industrialized countries. Breast cancer usually develops in perimenopausal and postmenopausal women, and only occasionally before age 25. In spite of many studies in the field, the mechanism of onset of breast cancer remains unknown. Multiple factors have been postulated to be involved, e.g., dietary habits, reproductive factors, and hormone

Correspondence to: *Prof. Nives Jonjić, MD, PhD*, Department of Pathology, School of Medicine, University of Rijeka, Braće Branchetta 20, HR-51000 Rijeka, Croatia
E-mail: nives@medri.hr

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disbalance. Familial susceptibility to the development of breast cancer suggests genetic predisposition as one of the candidate factors. Endogenous estrogen excess also plays a role in the onset of breast cancer, in particular in women with prolonged reproductive period, nulliparae and those with first delivery at an older age. Functional estrogen producing ovarian tumors are associated with the development of breast cancer, in postmenopausal women in particular. The exact mechanisms of estrogen effects on the genesis of breast cancer is not known, the more so as the normal breast tissue contains estrogen (ER) and progesterone (PR) receptors. It has been hypothesized that the interaction of circulating hormones, hormone receptors in tumor cells and autocrine growth factors produced by tumor cells may play a role in the progression of breast cancer. Some tumors, breast carcinoma and prostate carcinoma in particular, have been demonstrated to be sensitive to hormone effects, which is used in endocrine surgery and especially in therapy with drugs inhibiting hormone effects on tumor cells[1-3].

Steroid hormones show high specific binding to intracellular receptors that belong to a large protein family regulating transcription of other cell genes. Steroid receptors such as ER and PR are located in the cell nucleus. The hormones reach cell nucleus most probably by diffusion, and according to some authors by active transport; there they form the steroid-receptor complex that binds to the specific DNA segment located in the promoter region of the regulating gene[4]. Some steroid receptor regulated genes are involved in the regulation of cell growth and this effect is most likely to be considered responsible for the impact of ER on the behavior and treatment of breast cancer[5].

The aim of this study was to assess the frequency of ER and PR expression on tumor cells of invasive ductal carcinoma not otherwise specified (NOS) in patients treated at University Department of Surgery, Rijeka University Hospital Center, and to compare hormone dependence with the patient menopausal status and tumor histopathologic features such as tumor size and grade of differentiation.

Patients and Methods

The study included 549 patients that underwent mastectomy and were diagnosed with invasive ductal carcinoma (NOS) between January 1, 2000 and January 1, 2005. The median age of patients at diagnosis was 50 (range, 30-86) years. Among them, 135 (24.6%) were in premenopausal and 414 (75.4%) in postmenopausal status. The following parameters were observed: tumor size according to the American Joint Committee on Cancer (AJCC)[6]; degree of tumor histopathologic differentiation according to Bloom-Richardson-Elston modification; ER and PR status determined by immunohistochemistry; and carcinoma hormone dependence according to the expression of hormone receptors.

Table 1. Clinical, histopathology and immunohistochemistry parameters in patients with invasive ductal breast cancer (N=549)

Parameter	n (%)
Premenopause	135 (24.6)
Postmenopause	414 (75.4)
Tumor size*	
pT1	293 (53.4)
pT2	218 (39.7)
pT3	38 (6.9)
Histologic grade†	
GI	158 (28.8)
GII	304 (55.4)
GIII	87 (15.8)
Estrogen receptors	
Positive	396 (72.1)
Negative	143 (27.9)
Progesterone receptors	
Positive	383 (69.8)
Negative	166 (30.2)
Tumor hormone dependence‡	
1	345 (62.9)
2	89 (16.2)
3	115 (20.9)

*Size of invasive ductal carcinoma of the breast according to the American Joint Committee on Cancer (AJCC): pT1 <2 cm, pT2 2-5 cm, pT3 >5 cm in largest diameter;
†histopathologic grade of invasive ductal carcinoma of the breast: GI=well differentiated, GII=moderately differentiated, GIII=poorly differentiated carcinoma;
‡1 hormone dependent carcinoma: ER+PR+
2 probably hormone dependent carcinoma: ER+PR-; ER-PR+
3 hormone independent carcinoma: ER-PR-

Table 2. Hormone receptor expression in tumor cells of invasive ductal breast carcinoma according to menopausal status of study patients (N=549)

Menstrual status	n (%)			
	Estrogen receptors		Progesterone receptors	
	Positive	Negative	Positive	Negative
Premenopause	90 (66.7)	45 (33.3)	95 (70.4)	40 (29.6)
Postmenopause	306 (73.9)	108 (26.1)	288 (69.6)	126 (30.4)
*P**	0.103		0.860	

*χ^2-test

Statistics

The data obtained were processed by use of the Microsoft Word and Excel (version 11, Microsoft Corporation, Redmond, WA, USA) programs, and analyzed by statistical methods using χ^2-test and Fisher exact test in the absence of expected frequencies. The presence of statistically significant between-group differences was determined by parameter values ($P<0.05$). The SPSS for Windows (version 13.0, SPSS Inc., Chicago, IL, USA) program was employed on statistical analysis.

Results

The patient data collected and parameters observed are presented in Table 1. At the time of diagnosis, 75.4% of patients were in the postmenopausal period. In 53.4% of cases, the carcinoma measured less than 2 cm, corresponding to pT1 tumor size. Moderately differentiated carcinomas of histologic grade II were found in 55.4% and hormone dependent (ER+PR+) carcinomas in 62.9% of patients.

Tumor cell expression of hormone receptors (ER: $\chi^2=2.659$; df=1; $P=0.103$; and PR: $\chi^2=2.139$; df=1; $P=0.869$) showed no statistically significant differences according to the patient menopausal status (Table 2). Menopausal status had no impact on the rate of particular tumor stages according to TNM classification ($\chi^2=1.131$; df=2; $P=0.568$) or grade of histologic differentiation either ($\chi^2=0.390$; df=2; $P=0.823$) (Table 3).

However, in premenopausal women tumor size differed according to ER expression. Greater tumors classified as pT3 were more commonly ER- (85.7%), whereas pT1 (68.4%) and pT2 (71.2%) tumor stages were predominated by ER+ carcinoma (Fisher exact test=9.219; df=2; $P=0.012$). A similar pattern was also observed in case of PR, however, the difference did not reach statistical significance (Fisher exact test=6.194; df=2; $P=0.064$) (Table 4). In postmenopause, tumor size showed no statistically significant difference according to ER expression ($\chi^2=5.960$; df=2; $P=0.051$), but did show it according to PR expression. The major-

Table 3. Tumor size, histologic grade and hormone dependence according to menopausal status of study patients (N=549)

Menstrual status	n (%)								
	Tumor size			Histologic grade of differentiation			Hormone dependence‡		
	T1	T2	T3	GI	GII	GIII	1	2	3
Premenopause	76 (56.3)	52 (38.5)	7 (5.2)	36 (26.7)	77 (57.0)	22 (16.3)	82 (60.7)	23 (17.0)	30 (22.2)
Postmenopause	217 (52.4)	166 (40.1)	31 (7.5)	122 (29.5)	227 (54.8)	65 (15.7)	263 (63.5)	66 (15.9)	85 (20.5)
*P**	0.568			0.823			0.844		

*χ^2-test
‡1 hormone dependent carcinoma: ER+PR+
2 probably hormone dependent carcinoma: ER+PR-; ER-PR+
3 hormone independent carcinoma: ER-PR-

Table 4. Tumor size according to menopausal status of study patients (N=549)

	n (%)							
Tumor size	Premenopause				Postmenopause			
	ER+	ER–	PR+	PR–	ER+	ER–	PR+	PR–
pT1	52 (68.4)	24 (31.6)	55 (72.4)	21 (27.6)	171 (78.8)	46 (21.2)	161 (74.2)	56 (25.8)
pT2	37 (71.2)	15 (28.8)	38 (73.1)	14 (26.9)	115 (69.3)	51 (30.7)	110 (66.3)	56 (33.7)
pT3	1 (14.3)	6 (85.7)	2 (28.6)	5 (71.4)	20 (64.5)	11 (35.5)	17 (54.8)	14 (45.2)
P	0.012*		0.064*		0.051‡		0.044‡	

*Fisher exact test<, ‡χ^2-test

ity of pT1 (74.2%) and pT2 (66.3%) tumors were PR+, whereas pT3 tumors included an equal rate of PR+ and PR- cases (χ^2=6.225; df=2; *P*=0.044) (Table 4).

Tumor histologic grade differed significantly in premenopausal and postmenopausal patients according to the expression of ER (χ^2=28.162; df=2; and χ^2=55.287; df=2; respectively) and PR (χ^2=18.736; df=2; and χ^2=61.668; df=2; respectively) (*P*<0.001 all) (Table 5).

Tumor classification according to hormone dependence produced no significant differences between premenopausal and postmenopausal patients (χ^2=0.340; df=2; *P*=0.844) (Table 3). Yet, hormone dependent (ER+PR+) tumors had smaller diameter and were mostly of lower histologic grade, whereas hormone independent carcinomas (ER-PR-) were of a statistically significantly higher histologic grade (χ^2=15.263; df=4; *P*=0.004; and χ^2=97.593; df=4; *P*<0.001, respectively) (Table 6).

Discussion

Clinical outcome in patients with breast cancer is known to depend on a number of clinicopathologic factors such as metastatic status of lymph nodes, tumor size, histologic grade and histologic subtype of tumor, hormone receptor status, etc.[7-9]. In breast cancer, determination of ER and PR expression is essential not only for therapeutic response assessment but also for the prognosis of disease recurrence[10]. Generally, ER+PR+ tumors, classified as hormone dependent tumors, have better prognosis, and are less aggressive and less invasive than ER-PR-, hormone independent tumors, this variation being due to as yet incompletely clarified mechanisms[4,11]. In addition, the prognosis is hampered by the existence of so-called probably hormone dependent carcinomas, ER+PR-/ER-PR+, with unpredictable response to hormone therapy.

Table 5. Histologic grade of differentiation according to menopausal status of study patients (N=549)

	n (%)							
Histologic grade	Premenopause				Postmenopause			
	ER+	ER–	PR+	PR–	ER+	ER–	PR+	PR–
GI	26 (72.2)	10 (27.8)	28 (77.8)	8 (22.2)	107 (87.7)	15 (12.3)	107 (87.7)	15 (12.3)
GII	60 (77.9)	17 (22.1)	60 (77.9)	17 (22.1)	174 (76.7)	67 (29.5)	160 (70.5)	67 (29.5)
GIII	4 (18.2)	18 (81.8)	7 (31.8)	15 (68.2)	25 (38.5)	44 (67.7)	21 (32.3)	44 (67.7)
*P**	<0.001		<0.001		<0.001		<0.001	

*χ^2-test

Table 6. Tumor size and histologic grade of differentiation according to hormone dependence of carcinoma in study patients

n (%)						
Hormone dependence‡	Tumor size			Histologic grade of differentiation		
	pT1	pT2	pT3	GI	GII	GIII
1	195 (56.5)	135 (39.1)	15 (4.3)	124 (35.9)	203 (58.8)	18 (5.3)
2	50 (56.2)	29 (32.6)	10 (11.2)	20 (22.5)	48 (53.9)	21 (23.6)
3	48 (41.7)	54 (47)	13 (11.3)	14 (12.2)	53 (46.1)	48 (41.7)
*P**	0.004			<0.001		

‡1 hormone dependent carcinoma: ER+PR+
2 probably hormone dependent carcinoma: ER+PR-; ER-PR+
3 hormone independent carcinoma: ER-PR-

*χ^2-test

Results of the present 5-year study that included data on 549 patients with exclusively ductal invasive carcinoma (NOS), revealed ER and PR to be present in more than 60% of patients, which is consistent with literature data[12]. The expression of hormone receptors did not differ significantly according to menopausal status, in contrast to some literature reports. So, Pujoj *et al*.[13], and Ashba and Traish[14], using ligand binding assays on hormone status determination, found a higher rate of ER+ and ER+PR+ tumors in older age groups. In addition, Pujoj *et al*. report on a statistically significant difference in the expression of ER and PR in premenopausal women, depending on menstrual cycle, and higher levels of ER and PR in the follicular and ovulatory phase of the cycle, respectively. The potential reduction of ER+ tumors in premenopause the authors ascribe to the action of endogenous estrogen blocking ER, which is lost in postmenopause[13]. A higher prevalence of ER+PR+ carcinoma in older age groups has also been reported by Almasri and Al Hamad, associating the potential difference in ER and PR status between premenopausal and postmenopausal women with their different biology, which results in different hormone dependence[15]. However, it should be noted that variable study results might be due to different approaches in the selection of histologic tumor types, number of patients or methods of hormone receptor detection. So, immunohistochemistry has been reported to be superior to ligand binding assays for hormone receptor status determination[16].

Current concepts point to two ER forms, i.e. original ERα form and ERβ, encoded by two genes located on 6q25.1 chromosome for ERα and on 14q22-24 chromosome for ERβ[17,18]. It is also known that the expression of ERα varies during menstrual cycle and is generally detected at lower levels in normal tissue in premenopausal women[19]. An increase in ERα+ and Ki67 positive cell count has been reported in postmenopausal period[20]. Transformation of non-proliferating ERα+ cell phenotype to cells with strong ER expression and proliferation is postulated to be critical for the development of carcinoma. It is hypothesized that the error in ERα reduction leading to a higher percentage of positive cells and increase in ERα+ proliferating cells is regulated by some mechanisms that have not yet been identified[4].

In the present study, the size of ductal invasive breast carcinoma (NOS) correlated significantly with the expression of ER and PR. Tumors of greater diameter were mostly ER- in premenopausal women and PR- in postmenopausal women, which is consistent with literature data[8,21]. ER- carcinomas are postulated to develop from stem cells or ER- progenitor cells, whereas ER weakly positive tumors may develop from ER- progenitor and ER strongly positive tumors from ER+ progenitor[22]. Other authors speculate on ERα- tumors to arise from ER+ precursors that have ceased expressing the receptor after the initial phase[23]. Results of our study and other similar studies are in line with these hypotheses. After the initial phase, tumors of small diameter that mostly contain ER+ tumor cells produce ER- tumor cell clones by proliferation, and their proliferative activity is obviously regulated by some other mechanisms.

The grade of tumor cell differentiation also correlates with the expression of hormone receptors. In the present study as well as in other reports, poorly differentiated carcinomas were predominantly ER-

PR-, irrespective of the patient menopausal status[9,24]. The morphological and hormonal differences between well and poorly differentiated carcinomas were coupled with different gene expression between ER+ and ER- carcinomas as determined by DNA microarray technology[25]. The mechanisms regulating these variable gene expression call for further research, as they are of great importance for future studies of breast carcinoma.

As stated above, determination of ER and PR expression enables assessment of the tumor hormone dependence, which was the main objective of the study. ER is a known predictor of hormone therapy response[10], although there also are ER+ tumors that do not respond to this therapeutic modality. Patients with PR- tumors are known to respond less favorably to tamoxifen treatment[26]. PR is believed to be regulated by the ER gene, therefore PR expression points to functionally active ER[27]. However, the loss of PR may coincide with the presence of active ER, suggesting the possible complex action. PR is known to occur in two isoforms, A and B, the former being associated with tamoxifen resistance[28]. It is suggested that ERβ may also be involved in tamoxifen resistance[29]; however, other studies indicated its expression to correlate with better response to endocrine therapy and survival[30].

In conclusion, our retrospective study on invasive ductal carcinoma NOS showed no differences in the expression of steroid receptors and menopausal status. In addition, both pre- and postmenopausal women with poorly differentiated carcinomas were associated with ER-PR- status, while tumor size in premenopausal patients was mostly associated with ER and in postmenopausal women with PR status, which is consistent with literature data. Patient prognosis will be evaluated upon completion of the 5-year follow up period, with special reference to those with presumably hormone dependent carcinomas.

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Sažetak

IZRAŽENOST RECEPTORA ESTROGENA I PROGESTERONA U LJUDSKOM INAČE NESPECIFICIRANOM DUKTALNOM INVAZIVNOM KARCINOMU DOJKE: POSTOJI LI RAZLIKA IZMEĐU ŽENA U PREDMENOPAUZI I POSTMENOPAUZI?

J. Petričević, M. Petković i *N. Jonjić*

Određivanje hormonskih receptora iznimno je važno u planiranju liječenja kod bolesnica s rakom dojke. Cilj ove studije bio je procijeniti izraženost receptora estrogena (ER) i progesterona (PR) u inače nespecificiranom duktalnom invazivnom karcinomu dojke (NOS) u odnosu na menopauzalni status žene i histopatologiju tumora. U studiju je bilo uključeno 549 žena liječenih na Klinici za kirurgiju Kliničkog bolničkog centra Rijeka između 1. siječnja 2000. i 1. siječnja 2005. godine. Kod bolesnica je bio dijagnosticiran rak dojke i one su podvrgnute mastektomiji. Status ER i PR određen je imunohistokemijskim metodama. Rezultati nisu pokazali nikakvih značajnih razlika u izraženosti ER i PR, veličini tumora i stupnju histološke diferencijacije između žena u predmenopauzi i onih u postmenopauzi. Međutim, veličina tumora i stupanj histološke diferencijacije razlikovali su se značajno u odnosu na izraženost hormonskih receptora. Tumori veći od 5 cm uglavnom su bili ER- kod žena u predmenopauzi (P=0,012) i PR- kod onih u postmenopauzi (P=0,044). Slabo diferencirani karcinomi bili su udruženi sa statusom ER-PR- kod bolesnica u predmenopauzi kao i kod onih u postmenopauzi (P<0,001). Hormonski ovisni tumori (ER+PR+) bili su manjeg promjera i nižeg histološkog stupnja, dok su hormonski neovisni tumori (ER-PR-) imali veći promjer i viši histološki stupanj, i ta je razlika bila statistički značajna (P=0,004 odnosno P<0,001). Rezultati dobiveni za značajke duktalnog invazivnog karcinoma prema hormonskom statusu bili su sukladni onima u literaturi. S obzirom na proturječja o ulozi steroidnih receptora u endokrinom odgovoru na terapiju naš je budući cilj procijeniti 5-godišnju prognozu kod naših bolesnica.

Ključne riječi: *Karcinom, duktalni, dojka; Predmenopauza; Postmenopauza; Receptori estrogena; Receptori progesterona*