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CORRELATION BETWEEN STEROID RECEPTORS, ANGIOGENIC FACTORS, AND CLASSICAL PROGNOSTIC PARAMETERS IN NODE-NEGATIVE BREAST CANCER PATIENTS

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Abstract — Breast cancer (BC) progression is an estrogen receptor (ER) signaling- and angiogenesis-dependent process. This study investigated relationships between classical prognostic factors and biomarkers ER, PR, VEGF, and bFGF in node-negative BC patients. Positive correlation between ER and both PR ($p < 0.001$) or FGF ($p = 0.04$) levels indicates ER-regulated expression of these factors and a potential synergistic effect of ER and bFGF in tumor progression. Aside from correlation of age with ER and bFGF levels ($p = 0.003$; $p = 0.05$; respectively), no correlation of biomarkers with classical prognostic parameters was found, indicating that those biomarkers could be independent prognostic factors.

Key words: Breast cancer, prognosis, ER, PR, VEGF, bFGF

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INTRODUCTION

Breast cancer (BC) is the leading malignancy in women worldwide (Ahmedin, 2008). Classical prognostic factors (axillary lymph node status, tumor size, histological grade and type, patient's age and menopausal status) are still widely used as indicators of prognosis and therapeutic response in primary operable BC (Schnitt, 2001). Biological heterogeneity of BC results in the failure of traditional factors to predict precisely the occurrence of distant metastasis (Eppenberger et al., 1998), which is exemplified in the node-negative (pN0) group of BC patients. Metastases found in the regional lymph nodes are the most powerful prognostic indicators of poor BC patients' outcome (Schnitt, 2001). Still, they only indirectly reflect the process of hematogenic metastasis, since 20-30% of newly diagnosed pN0 BC patients will eventually develop distant metastases (McGuire and Clark, 1992). In addition, contrary to the consensus recommendation, the majority of pN0 patients will receive adjuvant therapy, which means that a large number of these patients is subjected to treatment with no evident benefit. There is therefore continuing interest in the investigation and validation of new prognostic biomarkers that could add prognostic value to classical prognostic factors and distinguish BC patients with low and high risk of disease recurrence.

Breast cancer is an estrogen-dependent disease, and enhanced activity of the estrogen receptor (ER) signaling pathway is considered to be a major driving force in tumorigenesis and BC progression (Colditz, 1998; Clemons and Goss, 2001; Murphy and Watson, 2002). In invasive BC, expression of the progesterone receptor (PR) is generally regarded as a marker of an intact ER signaling pathway (Horwitz and McGuire, 1975). During the last few decades, ER and PR were the most extensively studied molecular biomarkers. Their predictive value for the response to hormone therapy has been well established, while their prognostic role is controversial (Thorpe et al., 1993; Balleine, 2000, Hahnel and Spilsbury, 2004; Goldhirsch et al., 2007). In addition, the role of ER and PR in angiogenesis, the process involved in BC progression has been well studied, but is not yet clearly understood (Ali et al., 2000; Losordo and Isner, 2001; Dabrosin, 2005; Liang and Hyder, 2005).

Much evidence suggests that tumor development, progression, and metastasis in BC are angiogenesis-dependent (Gasparini, 2000). Tumor angio-

genesis involves an "angiogenic switch" that shifts the balance between pro- and anti-angiogenic signals towards the angiogenesis stimulatory signals (Hanahan and Folkman, 1996; Folkman, 2003). Estrogen-induced angiogenesis appears to occur due to the ability of ER to induce the expression of various angiogenic factors, such as VEGF and bFGF (Dabrosin, 2005). Since cancer cells can escape the primary tumor through both lymphatic and blood vessels, it is logical to presume that markers of neovascularization can add prognostic value to the classical prognostic factors in lymph node-negative BC patients.

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent pro-angiogenic factors involved in different stages of angiogenesis. Several experimental studies also suggested their stimulatory role in the growth of tumor cells (Keping, 2004; Presta, 2005). Functional estrogen response elements (EREs) in the gene coding for VEGF have been reported (Hyder, 2000). There is some evidence indicating that estrogen can regulate VEGF production in human breast cancer cells *in vitro* (Ruohola, 1999) and *in vivo* (Nakamura, 1996). The means by which estrogen induces bFGF expression are under study by several investigators. Stimulatory effects of estrogen on the production of bFGF and its receptor have been suggested (Lehtola, 1992). In general, there are consistent results (Gasparini, 1997; Eppenberger, 1998; Linderholm, 1998, 2000; Coradini, 2001; Manders, 2002) regarding the relationship between increased VEGF values and poor prognosis (in terms of DFI) of pN0 breast cancer patients who were not treated with adjuvant therapy, while the results concerning bFGF are contradictory (Colomer, 1997; Blanckaert, 1998; Eppenberger, 1998; Faridi, 2002).

This study was aimed at investigating relationships between the classical prognostic parameters (tumor size, histological type, patients' age and menopausal status) and potential biomarkers such as steroid receptors (ER, PR) and angiogenic factors (VEGF and bFGF) in a group of pN0 BC patients who received no adjuvant therapy.

PATIENTS AND METHODS

The study included 92 patients with histologically verified node-negative primary operable breast carcinomas. None of the patients received adjuvant therapy. The natural course of the disease was followed for a period of 12 years for each individual patient in such a way that the patients' follow-up was conducted every 3 months for the first 18 months, then monthly for 3 years, and yearly thereafter.

Clinicopathological prognostic parameters: Age and menopausal status as tumor-host parameters

Table 1. Clinicopathological characteristics of patients and tumors.

	Total group of patients	
Characteristic	N = 92	%
Age (median, range)	57 (41-79) years	
41-59 years	52	56.5
>59 years	40	43.5
Menopausal status		
pre	22	23.9
post	70	76.1
Tumor size		
pT1 (< 2cm)	53	57.6
pT2 (≥ 2cm)	37	40.2
pTx	2	2.2
Histological type		
IDC	38	41.3
ILC	27	29.3
other	27	29.3

and tumor size (pT), regional lymph node status (pN), and histological type as tumor parameters were obtained with Institutional Review Board approval. A patient was considered to be premenopausal when the menstrual cycles still persisted or postmenopausal if menstruation ceased for at least six months. Histological specimens were reviewed and then classified according to the criteria of the International Union Against Cancer for TN stages (UICC, 1987) and histological type (Scarf and Torloni, 1968). Clinicopathological parameters of patients and tumors are shown in Table 1.

Molecular prognostic parameters: Estrogen receptor quantitative values were measured by the classical biochemical method as recommended by the EORTC (EORTC, 1980). Intralaboratory quality assessment of ER quantitative values was performed periodically according to the EORTC recommendation (Romain et al., 1995). Concentration of VEGF (Span et al., 2000) and bFGF (Colomer, 1997) in the cytosol fraction of tumors were analyzed by immunometric assays (R & D Systems, Minneapolis, MN). Quantitative values of molecular prognostic biomarkers ER, PR, bFGF, and VEGF are presented in Table 2. The Kolmogorov-Smirnov test showed that the distributions of quantitative values of the molecular biomarkers were significantly different from the normal distribution, and nonparametric statistical tests were therefore applied in further analysis.

Statistical evaluations: In order to analyze differences between quantitative values of biomarkers in patients' subgroups as defined by classical prognostic parameters, the Mann-Whitney's rank sum test was applied. The Spearman correlation test was used to test correlations between quantitative values of parameters. A probability (p) level of less than 0.05 was selected as the threshold of statistical significance.

RESULTS

Correlations between molecular prognostic markers

A strong positive correlation was found between ER and PR quantitative values in the whole group of pN0 BC patients ($n = 92$, $p < 0.001$) (Fig. 1) and similarly between ER and bFGF protein values ($n = 91$, $p = 0.04$) (Fig. 2). We found no correlation between ER and VEGF protein values. In addition, no correlation was found between PR, bFGF, and VEGF quantitive values. Analysis of correlation between molecular biomarkers and classical prognostic parameters revealed that only ER expression was significantly correlated (positively) with the age of patients ($n = 92$, $p = 0.002$).

Correlations between molecular and classical prognostic biomarkers

Analysis of quantitative values of biomarkers (Table 3) revealed that the median ER level was significantly higher in older (> 59 years, $n = 40$) than in younger (41-59 years, $n = 52$) patients ($p = 0.003$), while no difference was found between median ER levels in groups of patients defined by tumor size, histological type, or menopausal status. In the same way, the median bFGF level was significantly higher in older (> 59 years, $n = 39$) than in younger (41-59 years, $n = 51$) patients ($p=0.05$), while there was no difference in median bFGF levels between groups of

Table 2. Concentrations of molecular biomarkers.

		Concentration		
Biomarker	**No. of patients**	**median**	**range**	**units**
ER	92	28	0-772	fmol/mg
PR	92	6	0-154	fmol/mg
bFGF	90	98.7	2.2-829.4	pg/mg
VEGF	78	240	40-6130	pg/mg

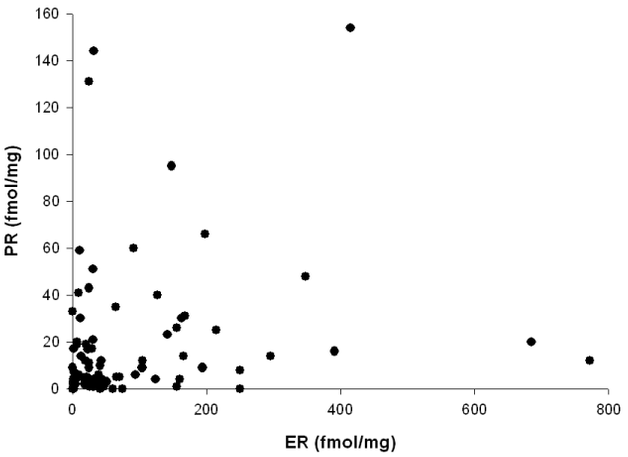

Fig. 1. Correlation between ER and PR quantitative values in pN0 BC patients (n = 92, p < 0.001).

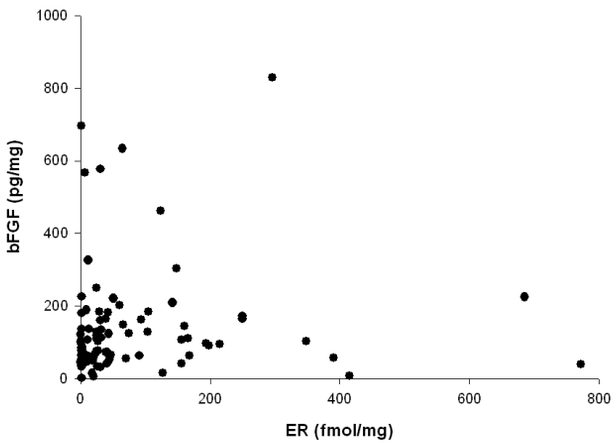

Fig. 2. Correlation between ER and bFGF quantitative values in pN0 BC patients (n = 91, p = 0.04).

Table 3. Comparison of ER, PR, bFGF, and VEGF quantitative values between groups.

	N	median, range	*P*-value
Parameter	**ER (fmol/mg)**		
Tumor size			
pT1	53	27 (0-250)	
pT2	37	32 (1-772)	0.24
Menopausal status			
pre	22	19 (0-168)	
post	70	36 (0-772)	0.09
Age			
≤ 59 years	52	20 (0-685)	
> 59 years	40	63 (1-772)	0.003
Histological type			
IDC	38	27 (0-772)	
ILC	27	32 (0-685)	0.44
Parameter	**PR (fmol/mg)**		
Tumor size			
pT1	53	5 (0-144)	
pT2	37	14 (1-154)	0.20
Menopausal status			
pre	22	16.5 (0-144)	
post	70	5.5 (0-154)	0.12
Age			
≤ 59 years	52	4.5 (0-154)	
> 59 years	40	9 (0-95)	0.30
Histological type			
IDC	38	5.5 (0-144)	
ILC	27	9 (0-95)	0.53
Parameter	**bFGF (pg/mg)**		
Tumor size			
pT1	51	100.7 (5.8-577.4)	
pT2	37	102.7 (2.2-829.4)	0.53
Menopausal status			
pre	22	70.2 (14.4-566.3)	
post	68	101.7 (2.2-829.4)	0.19
Age			
≤ 59 years	51	81.4 (5.8-696.4)	
> 59 years	39	111.1 (2.2-829.4)	0.05
Histological type			
IDC	37	106.1 (5.8-696.4)	
ILC	26	126.8 (32.3-633.6)	0.45
Parameter	**VEGF (pg/mg)**		
Tumor size			
pT1	44	200 (50-1460)	
pT2	32	340 (40-6130)	0.15
Menopausal status			
pre	19	300 (80-1730)	
post	59	200 (40-6130)	0.20
Age			
≤ 59 years	43	280 (60-3190)	
> 59 years	35	120 (40-6130)	0.09
Histological type			
IDC	31	170 (40-4630)	
ILC	27	240 (40-750)	0.54

patients defined by tumor size, histological type, or menopausal status. Unlike ER and bFGF, we found no difference of median PR and VEGF values between groups of patients defined by tumor size, histological type, menopausal status, or age of patients.

DISCUSSION

Prediction of development of distant metastases represents a very relevant research end point since they are the major cause of death in BC patients. Distant metastases can develop after off-lining of primary tumor cells through both hematogenic and lymphogenic pathways. After removal of a primary breast carcinoma, relapse represents the major problem in the management of patients, since latent micrometastases often remain asymptomatic and clinically undetectable for a long time. Therefore, the main goal of investigators worldwide is to find parameters that can indicate the presence of micrometastases and/or predict their progression into clinically detectable macrometastases.

The first generation of prognostic parameters is insufficient to predict patients' outcome and that is why adjuvant systemic therapy is offered to all node-negative breast cancer patients, the group with a very favorable prognosis. The goal of our research was focused on molecular biomarkers as potential prognostic factors in the group of pN0 BC patients who were not treated with adjuvant therapy. We

investigated the relationships between steroid receptors (ER, PR), angiogenic factors (bFGF, VEGF), and classical prognostic parameters in order to select those that could be used independently in analyzing the natural course of the disease.

The first step in our analysis was to explore relationships between quantitative values of the analyzed biomarkers. The obtained ER quantitative values correlated positively with PR values, which is in line with the well-known fact that PR expression is ER-regulated and indicates the existence of an intact ER-signaling pathway (Horwitz and McGuire, 1975). Our finding that bFGF values positively correlated with ER values confirms the results of other authors (Smith et al., 1999) regarding possible regulation of bFGF expression via ER (Lehtola et al., 1992; Dabrosin, 2005), through either an estrogen-dependent or an estrogen-independent pathway. Furthermore, it indicates a possible synergistic effect of ER and bFGF in the processes of angiogenesis and tumor progression. The finding that there was no correlation between ER and VEGF is not opposed to the finding that ERE exist within the VEGF promotor, but suggests the importance of post-translational regulation of VEGF expression, as well as the availability of tissue VEGF to detected antibodies (Dabrosin, 2005).

The second step in our analysis was to compare quantitative values of the analyzed biomarkers in different groups of patients defined by classical prognostic factors (tumor size, histological type, age of patients, and menopausal status). Our results show that the selected molecules were independent of traditional parameters, which, in addition to published data, indicates their possible prognostic value in BC. The ER and bFGF factors were the only ones that correlated with some of classical parameters, and their levels were significantly increased in the group of patients older than 59 years, which is in line with the published data for ER (Clark et al., 1984; Shek and Godolphin, 1989; Hanahan and Folkman, 1996), but not established for bFGF (Smith et al., 1999). Estrogen levels are known to be low and constant in the group of patients older than 59 years (at the time of surgery) (Hanahan and Folkman, 1996), since they are all postmenopausal. It has been hypothesized (Osborne, 1998) that the growth of micrometastasis in this group of patients is controlled by the overexpression of unliganded ER, which influences the protein expression of target genes via a noncanonical mechanism.

The findings from this experimental study will be used in clinical analysis of the natural course of the disease in the same group of pN0 BC patients. Analysis of survival in relation to classical prognostic parameters and biological markers (ER, PR, bFGF, and VEGF) will be performed in the whole group of patients. Special attention will be paid to the group of patients older than 59 years, in which we could exclude the effect of estrogen-regulated expression of the analyzed biomarkers on their prognostic importance and explore the impact of increased levels of ER and bFGF in the prognosis of pN0 BC patients.

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КОРЕЛАЦИЈЕ ИЗМЕЂУ СТЕРОИДНИХ РЕЦЕПТОРА, ФАКТОРА АНГИОГЕНЕЗЕ И КЛАСИЧНИХ ПАРАМЕТАРА ПРОГНОЗЕ У КАНЦЕРА ДОЈКЕ У ГРУПИ ПАЦИЈЕНАТА БЕЗ МЕТАСТАЗА У РЕГИОНАЛНИМ ЛИМФНИМ ЧВОРОВИМА

ТИЈАНА ВУЈАСИНОВИЋ, М. МАРКИЋЕВИЋ, З. АБУ РАБИ и ДРАГИЦА НИКОЛИЋ-ВУКОСАВЉЕВИЋ

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Прогресија карцинома дојке је процес који зависи од сигналног пута рецептора за естроген (ЕР) и ангиогенезе. Васкуларни ендотелијални фактор раста (ВЕГФ) и базни фактор раста фибробласта (бФГФ) су најпотентнији проангиогенезни фактори. Ова студија је испитивала односе класичних фактора прогнозе и потенцијалних биомаркера, ЕР, ПР, ВЕГФ и бФГФ, у групи пацијената оболелих од канцера дојке код којих нису нађене малигне ћелија у регионалним лимфним чворовима. Позитивна корелација између нивоа ЕР и ПР ($п < 0.001$) и ФГФ ($п = 0.04$) указује на регулацију експресије ових фактора естрогеним рецептором и могућу синергистичку улогу ЕР и бФГФ у прогресији тумора. Осим корелације година са нивоима ЕР и бФГФ ($п = 0.003$ и $п = 0.05$, респективно), нису нађене друге корелације анализираних биомаркера са класичним прогностичким параметрима што указује да би ти биомаркери могли да буду независни прогностички фактори.