SPANDIDOS PUBLICATIONS

Prognostic significance of insulin growth factor-I receptor and insulin growth factor binding protein-3 expression in primary breast cancer

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Abstract. We analyzed insulin-like growth factor receptor I (IGF-IR) and insulin growth factor binding protein-3 (IGFBP-3) expression with respect to overall survival and relapse-free survival (RFS) in 460 patients with primary invasive breast cancer using immunohistochemistry. IGF-IR expression had a significant positive correlation with positive estrogen receptor (ER), positive progesterone receptor (PR) and Bcl-2 expression. Univariate analysis showed significantly better overall survival (p=0.000) and RFS (p=0.004), in the IGF-IR-positive group. Multivariate analysis showed a significant reduction in relative risk for overall survival (p=0.019, HR=0.221, 95% CI=0.062-0.780) and RFS (p=0.026, HR=0.462, 95% CI=0.234-0.913) in the IGF-IR-positive group. IGF-IR expression in primary breast cancer is an independent favorable prognostic factor. IGFBP-3 expression in breast cancer is associated with poor outcome.

Introduction

High blood IGF-I levels are associated with an increased risk of breast cancer, especially in premenopausal women (1). Most of the effects of IGF-I result from its activation of the IGF-IR. The insulin-like growth factors (IGFs) are mitogens that play a pivotal role in regulating cell proliferation, differentiation, and apoptosis. The effects of IGFs are mediated through the IGF-I receptor. The IGFs are modulated by a family of six high-affinity IGF binding proteins, of which IGFBP-3 predominates in serum and is upregulated in breast cancer cell lines, including breast epithelium. Both IGFs (IGF-I and IGF-II) have a preferential stromal expression and together with epithelial IGFBP-3 have a significant paracrine influence on breast epithelial growth (2). IGFBP-3 is found not only to regulate the mitogenic action of IGFs but also to inhibit their anti-apoptotic effect. Besides its IGF-dependent function, IGFBP-3 also has an IGF independent inhibitory effect on cell growth (3).

The IGF-IR activation has been implicated in the malignant progression of several types of human cancer (4,5). IGF-IR has been found to be significantly expressed and highly activated in breast cancer, and its prognostic and predictive value in clinical samples is of interest (6-8). However, the correlation between IGF-IR overexpression and prognosis or other clinicopathological parameters has not been confirmed (9,10). Detection of IGFBP-3 in breast tissue has been reported to have no association with disease-free survival and to have either no association with overall survival or an association with increased risk of death; the latter association was independent of other prognostic factors (11,12).

We analyzed the immunohistochemical expression of IGF-IR and IGFBP3 with clinicopathological variables and the correlation with overall survival and relapse-free survival (RFS) in 460 patients with invasive breast cancer.

Patients and methods

Patients. Four hundred and sixty patients (median age 46; age range, 23-84 years) with breast carcinomas were included in this study. The patients underwent breast cancer surgery at the National Cancer Center (Gyeonggi, Korea) and at Kangbuk Samsung Hospital (Seoul, Korea) between 2000 and 2006. Three hundred and twenty-eight of the patients with breast cancer underwent survival analysis. The mean follow-up was 53 (range 7-85) months. The immunohistochemical expression of IGF-IR and IGFBP-3 was analyzed in 460 patients with breast cancer. The RFS was calculated as the period from surgery until the date of the first recurrence. The study was submitted and met the guidelines of the local institutional review committees.

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Abbreviations: IGF-IR, insulin-like growth factor receptor I; IGFBP-3, insulin growth factor binding protein-3; ER, estrogen receptor; PR, progesterone receptor; BMI, body mass index; BCO, breast conserving surgery; HER2, human epidermal growth factor receptor 2; EGFR, epithelial growth factor receptor; VEGF, vascular endothelial growth factor; OS, overall survival; RFS, relapse-free survival; RR, relative risk; CI, confidence interval

Key words: breast cancer, IGF-IR, IGFBP-3, immunocytochemistry

Table I. Correlation for IGF-IR and IGFBP-3 expression with clinicopathological variables in primary breast cancer.

		IGF-IR					IGFBP-3				
		Negative		Positive			Negative		Positive		
	Total	n	%	n	%	P-value	n	%	n	%	P-value
Age											
<50	275	131	58.0	144	63.4	0.233	147	62.8	111	61.7	0.810
≥50	178	95	42.0	83	36.6		87	37.2	69	38.3	
BMI											
<25	162	79	35.0	83	36.6	0.744	82	35.0	69	38.3	0.575
≥25	56	26	11.5	30	13.2		32	13.7	19	10.6	
Operation											
BCO	95	47	20.8	48	21.1	0.271	33	14.1	51	28.3	0.001
Mastectomy	303	157	69.5	146	64.3		177	75.6	106	58.9	
Histological grade											
1	101	42	19.6	59	27.8	0.014	56	25.0	33	19.9	0.444
2	173	82	38.3	91	42.9		89	39.7	67	40.4	
3	152	90	42.1	62	29.2		79	35.3	66	39.8	
T											
T1	223	108	47.8	115	50.7	0.211	103	44.0	96	53.3	0.204
T2	197	96	42.5	101	44.5		112	47.9	72	40.0	
T3	29	20	8.8	9	4.0		18	7.7	10	5.6	
T4	4	2	0.9	2	0.9		1	0.4	2	1.1	
N											
N0	265	127	56.2	138	60.8	0.025	128	54.7	115	63.9	0.117
N1	106	47	20.8	59	26.0		57	24.4	39	21.7	
N2	38	27	11.9	11	4.8		27	11.5	10	5.6	
N3	44	25	11.1	19	8.4		22	9.4	16	8.9	
ER											
Negative	206	148	66.1	58	25.6	0.000	103	44.0	88	49.4	0.274
Positive	245	76	33.9	169	74.4		131	56.0	90	50.6	
PR											
Negative	221	152	67.9	69	30.4	0.000	106	45.3	95	53.1	0.117
Positive	230	72	32.1	158	69.6		128	54.7	84	46.9	
HER2											
No overexpression	359	154	68.8	205	90.3	0.000	196	83.8	134	74.9	0.025
Overexpression	92	70	31.3	22	9.7		38	16.2	45	25.1	
Hormone therapy											
No	88	63	37.7	25	15.6	0.000	34	19.5	47	36.2	0.001
Yes	239	104	62.3	135	84.4		140	80.5	83	63.8	
Chemotherapy											
No	59	19	11.4	40	25.0	0.001	31	17.8	23	17.7	0.978
Yes	268	148	88.6	120	75.0		143	82.2	107	82.3	

Standard histopathological examination included the type of cancer and the pathological tumor stage assessed according to the criteria established by the 6th edition of the AJCC Staging Manual (13).

H&E and immunohistochemical staining. All of the tissues obtained from patients were routinely fixed in 10% buffered formalin and embedded in paraffin blocks. Tissue array blocks containing breast cancer tissues (6 mm in diameter) were produced from enrolled cases. The tissue microarray blocks were sectioned at a thickness of 4-μm and were processed for immunohistochemical staining. Paraffin was removed from the tissue sections with xylene. The sections were rehydrated with graded ethanol and immersed in Tris-buffered saline. The expression of IGF-IR, IGFBP-3, and VEGF was determined by immunohistochemical staining using rabbit poly-

Correlation for IGF-IR and IGFBP-3 expression with breast cancer-related biomarkers.

	IGF-IR					IGFBP-3				
	Negative		Positive			Negative		Positive		
	n	%	n	%	P-value	n	%	n	%	P-value
EGFR										
Negative	179	83.6	192	91.4	0.015	196	87.5	153	89.0	0.658
Positive	35	16.4	18	8.6		28	12.5	19	11.0	
VEGF										
Negative	135	63.1	151	71.9	0.053	150	66.7	122	69.7	0.517
Positive	79	36.9	59	28.1		75	33.3	53	30.3	
Bcl2										
Negative	134	62.0	56	25.3	0.000	91	39.6	86	49.1	0.054
Positive	82	38.0	165	74.7		139	60.4	89	50.9	
p53										
Negative	141	65.6	181	81.2	0.000	169	73.8	126	71.6	0.620
Positive	74	34.4	42	18.8		60	26.2	50	28.4	
Ki-67										
Low (<10%)	134	66.7	154	72.6	0.186	157	71.4	110	65.5	0.215
High (≥10%)	67	33.3	58	27.4		63	28.6	58	34.5	
IGFBP-3										
Negative	111	53.9	123	59.4	0.256	234	100	0	0	
Positive	95	46.1	84	40.6		0	0	180	100	
IGF-IR										
Negative	226	100	0	0		111	47.4	95	53.1	0.256
Positive	0	0	227	100		123	52.6	84	46.9	

clonal antibodies against IGF-IRß (1:100 dilution; Cell Signaling Technology, Danvers, MA), goat polyclonal antibodies against IGFBP-3 (C-19, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and mouse monoclonal antibodies against VEGF (C-1, 1:100 dilution; Santa Cruz Biotechnology). A biotinylated anti-mouse antibody was used as a secondary antibody, and streptavidin horseradish peroxidase (Zymed Laboratories, San Francisco, CA, USA) was used following the instructions provided by the manufacturer. The sections were counterstained in Mayer's hematoxylin, dehydrated and cleared, and the sections were mounted for examination (Fig. 1).

Interpretation of immunohistochemistry findings. Immunoreactivity for IGF-IR was evaluated in the neoplastic epithelial cells using a combined scoring system based on the sum of the staining intensity (0, negative staining; 1, weak; 2, intermediate; and 3, strong staining) and the percentage of positive cells (0, 0%; 1, 1-25%; 2, 26-50%; and 3, >50%). Scores from 0-3 were given for the staining intensity and the percentage of positive cells, these then being added together to obtain the overall score with a maximum of 6. A score of 0 (negative or low expression) was considered as negative with respect to IGF-IR staining, while scores of 2-6 (high expression) were considered as positive (14).

IGFBP-3 expression was scored as follows: the staining intensity in the cytoplasm only was evaluated from 0 to 3 (representing none to strong staining, respectively) and the % cells in each intensity was obtained. The overall score was determined as follows: overall score = [(% cells with visual score 1) x 1] + [(% cells with visual score 2) x 2] + [(% cells with visual score 3) x 3]; expression was positive if the score was >5 (15).

A cut-off value of 10% of the positively-stained nuclei was used to define estrogen receptor (ER) and progesterone receptor (PR) positivity. Cytoplasmic staining with an intensity >10% of the tumor cells was scored as positive for Bcl-2. Membranous staining for HER2 was scored as follows: 0, no staining or membranous staining in <10% of the cells; 1+ , faint incomplete staining in 10% of the cells; 2+, weak-to-moderate complete staining in 10% of the cells; and 3+, strong complete staining in 10% of the cells. HER2 overexpression was defined as a score of 3+. Cells staining for Ki-67 and p53 were expressed as a percentage. The Ki-67 labeling index was graded as low if the number of positive cells was <10% and high if the number of positive cells was ≥10%. p53 was scored as positive if >10% of the cells were positive with a strong intensity.

Statistical analysis. Statistical analysis was performed with SPSS software, version 15.0 (SPSS, Inc., Chicago, IL, USA). Pearson's χ^2 test was used to examine the correlation between the variables. Kaplan-Meier curves were plotted from data of the overall survival and RFS. The Cox proportional regression hazard model was performed with variables, including histological grade, ER expression, PR expression, HER2 over-

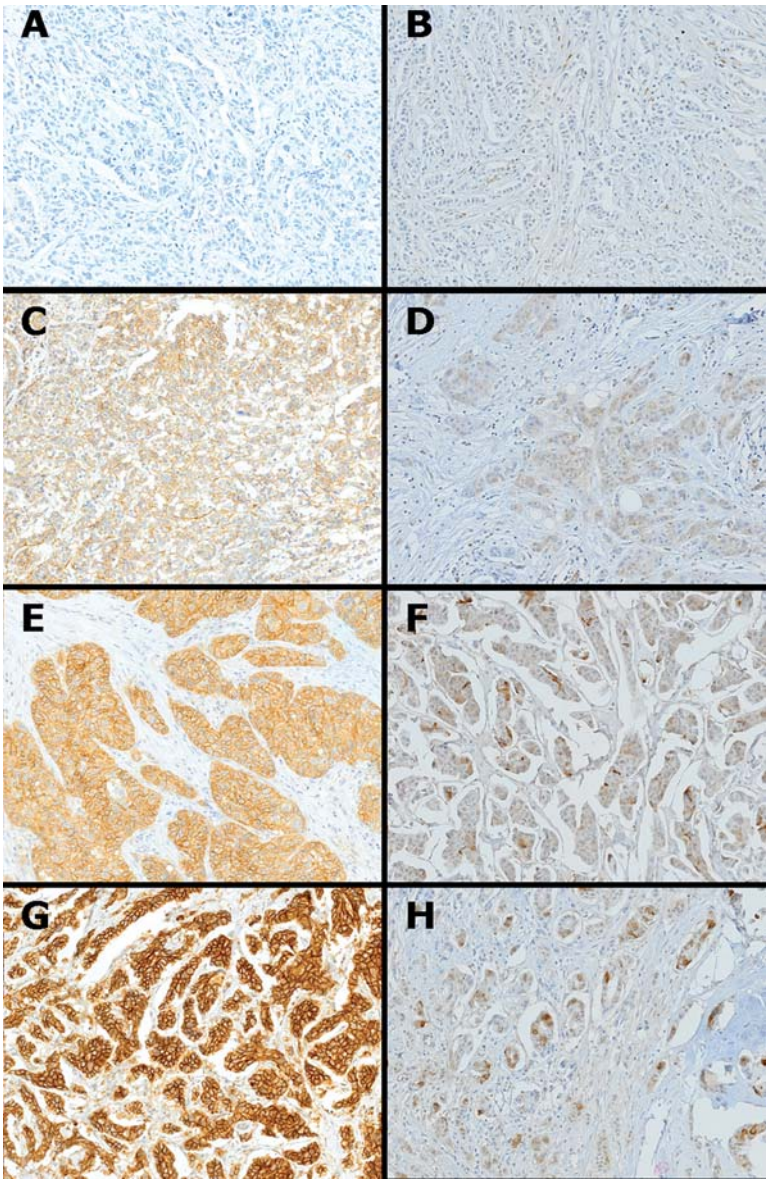

Figure 1. Immunohistochemical detection of IGF-IR and IGFBP-3 in breast cancer tissues. (A, C, E and G) IGF-IR. (B, D, F and H) IGFBP-3. (A and B, negative; C and D, weak positive; E and F, moderate positive; G and H, strong positive).

expression, IGF-IR expression, IGFBP-3 expression, hormone therapy and chemotherapy for survival analysis. A p-value <0.05 was considered statistically significant.

Results

Clinicopathological correlation of IGF-IR and IGFBP-3 expression in breast cancer tissue. The clinicopathological characteristics of the enrolled patients and correlation for IGF-IR and IGFBP-3 expression is shown in Table I. Positive membrano-cytoplasmic immunoreactivity for IGF-IR existed in 50.1% of the cases (227 of 453). Cytoplasmic expression for IGFBP-3 was noted in 43.5% (180 out of 414). IGF-IR expression had a significant correlation with ER, PR, and a significant inverse correlation with histological grade, N stage and HER2 overexpression. IGFBP-3 expression had a significant correlation with HER2 overexpression. However, no significant correlation was noted for age, BMI, or T stage with IGF-IR or IGFBP-3 expression. In the comparison with expression of breast cancer-related markers, the expression of IGF-IR correlated with Bcl-2 expression (p=0.000) and was inversely correlated with p53 (p=0.000) and EGFR expression (p=0.015); no significant correlation was noted with IGFBP-3 expression (Table II).

Univariate analysis of IGF-IR and IGFBP-3 expression on overall survival and RFS in breast cancer patients. Based on the univariate Kaplan-Meier analysis of 326 cases, the clinicopathological variables with a prognostic value included histological grade, T stage, N stage, HER2 status, and Bcl-2, p53, or Ki-67 expression for overall survival; T stage, N stage, HER2 status, and p53 expression for relapse-free survival (RFS) (data not shown).

Kaplan-Meier survival analyses showed a significantly better overall survival (p=0.000) and RFS (p=0.004) in the IGF-IR-positive group compared to the IGF-IR-negative group. In contrast, IGFBP-3-positive group showed worse overall survival (p=0.057) and no difference in RFS compared to IGFBP-3-negative group (Fig. 2). We stratified the patients

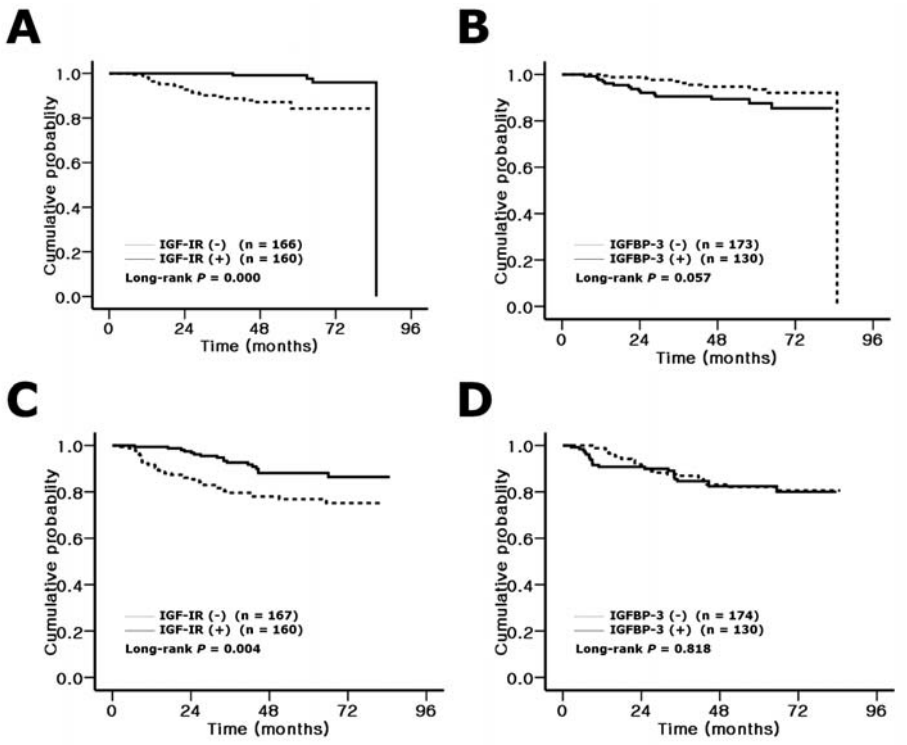

Figure 2. Overall survival (A) and RFS (B) according to IGF-IR; overall survival (C) and RFS (D) according to IGFBP-3 in patients with breast cancer.

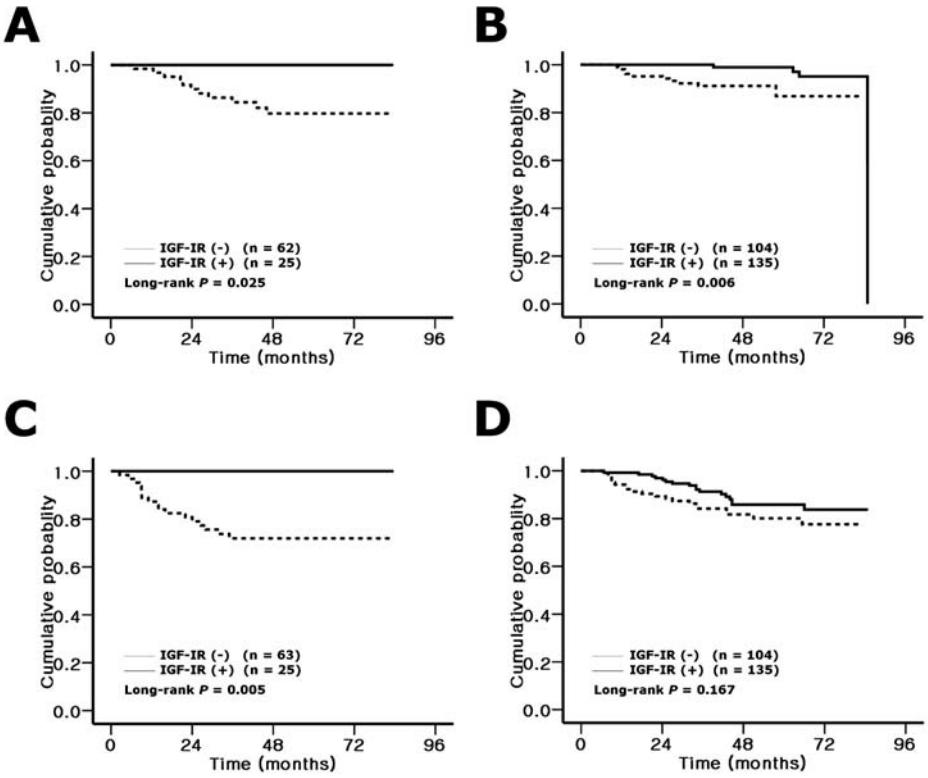

Figure 3. Overall survival and RFS in subgroup analyses by hormone therapy. Overall survival in (A) no hormone therapy, (B) hormone therapy; RFS in (C) no hormone therapy, (D) hormone therapy.

by whether they received hormone therapy or not. Both the patient groups with hormone therapy and without hormone therapy showed significant difference of overall survival. Between the patient groups with IGF-IR-positive and negative, a significant difference in RFS was noted in the patients without hormone therapy, not in the patients with hormone therapy (Fig. 3). The difference of 5-year overall survival by IGF-IR expression was greater in the group with hormone therapy (20.3%) than without hormone therapy (12.3%). The difference of 5-year RFS by IGF-IR expression was greater in the group with hormone therapy (28.2%) than without hormone therapy (5.9%, Fig. 3).

Table III. Cox's proportional hazards regression models for overall survival and RFS.

		Overall survival			RFS		
	n	RR	95.0% CI	P-value	RR	95.0% CI	P-value
Histological grade							
1/2	175	1.526	0.644-3.617	0.337	0.961	0.513-1.800	0.902
3	108						
ER							
Negative	136	0.706	0.208-2.398	0.577	1.081	0.483-2.419	0.850
Positive	147						
PR							
Negative	143	0.284	0.070-1.153	0.078	0.635	0.290-1.392	0.257
Positive	140						
HER2							
No overexpression	225	1.538	0.674-3.507	0.306	1.861	0.988-3.504	0.055
Overexpression	58						
IGF-IR							
Negative	147	0.221	0.062-0.780	0.019	0.462	0.234-0.913	0.026
Positive	136						
IGFBP-3							
Negative	46	2.151	0.937-4.939	0.071	1.089	0.607-1.952	0.776
Positive	237						
Hormone therapy							
No	75	1.502	0.601-3.756	0.384	1.346	0.636-2.847	0.437
Yes	208						
Chemotherapy							
No	164	2.585	0.333-20.044	0.363	491608	0.000-1.7E+217	0.958
Yes	119						

Multivariate analysis. A model of multivariate Cox proportional hazard analysis was performed with variables, including IGF-IR expression and IGFBP-3 expression (Table III). A model adjusted for histological grade, ER expression, PR expression, HER2 overexpression, IGF-IR expression, IGFBP-3 expression, hormone therapy and chemotherapy showed a significant reduction of relative risk by IGF-IR expression for overall survival (p=0.019, HR=0.221, 95% CI=0.062-0.780) and for RFS (p=0.026, HR=0.462, 95% CI=0.234-0.913). However, no significant correlation was noted by IGFBP-3 expression for overall survival or RFS in this model (Table III).

Discussion

IGF-IR is overexpressed in colorectal cancer and synovial sarcoma, and its overexpression is associated with aggressive tumors (16,17). Previous studies were not consistent regarding the intratumoral IGF-IR expression as a prognostic factor in primary breast cancer. Expression of IGF-IR was associated with a poor prognosis in the subgroup of ER-negative cancers (18), or to be without prognostic importance (8). Nielsen *et al* (19) noted IGF-IR immunostaining in 87% in breast cancer (615 of 707) and they reported that the expression of IGF-IR and urokinase plasminogen activator is associated with poor survival. Shin *et al* (20) reported the reduced mRNA expression of IGF-I and IGF-IR genes in breast tumor tissue compared to adjacent tissue and a correlation for poor overall and disease-free survival. Increased level of IGF-IR expression in breast cancer specimens is found to inhibit apoptosis, and was associated with an increased risk of relapse after radiation therapy (21). There are studies concordant with our results that reported that the expression of IGF-IR was associated with a better overall survival and RFS by immunoassay (7,22). Our study strongly suggested that intratumoral IGF-IR expression is a significant prognostic factor and intratumoral IGFBP-3 expression is associated with a shorter overall survival in breast cancer by immunohistochemistry.

Shimizu *et al* (9) showed no correlation for IGF-IR expression and prognosis using antibody against IGF-Iα. IGF-IR is a tetramer composed of two extracellular α-subunits (130 kDa) and two transmembrane ß-subunits (90 kDa). The α-subunit is extracellular, while the ß-subunit is a transmembrane protein that has cytoplasmic tyrosine kinase activity. IGF-I binding to the extracellular domain stimulates tyrosine kinase activity, which in turn phosphorylates cytoplasmic components of an IGF-I-specific signal cascade leading to several biological effects, including cell growth (7). It should be noted that IGF-IR immunostaining with a single ß-subunit antibody was diffusely cytoplasmic in most samples, in contrast to the expected membrane localization

by Chott *et al* (23), who used two different α-subunit antibodies.

IGF-IR ligands, IGF-I and IGF-II are strong mitogens for many hormone-dependent breast cancer cell lines and have been found in the epithelial and/or stromal component of breast tumors. During tumorigenesis, overexpression of IGF-IR is presumed to increase the cellular responsiveness to IGFs in terms of proliferation and inhibition of apoptosis (24). In breast cancer cells, estrogens enhance the mitogenic effect of IGF-I, induce expression of IGF-I, and stimulate production of IGF-IR (3). The interaction between estrogens and IGF is reciprocal. IGF-I enhances expression of estrogen receptor in breast cancer cells, and ER levels in breast tissue are associated with the levels of some IGFBPs (3).

Our results showed that IGF-IR could be an indication of the tamoxifen-resistance in the patients who received adjuvant hormone therapy, because the group with hormone therapy showed less survival gain by IGF-IR expression compared to the group without hormone therapy. One study for utilization of semi-quantitative immunohistochemistry of IGF-IR as one of the markers of intratumoral ER showed promising results for prediction of response to letrozole versus tamoxifen (25). They showed that the greatest benefit from aromatase inhibitor treatment was seen in patients with a high expression level of estrogen regulated proteins such as PR, Bcl-2 and IGF-IR reflecting a high intratumoral estrogen content and ER driven cell growth.

In cancer, IGFBPs regulate the action of IGFs. In most situations, the binding proteins suppress the mitogenic action of IGFs and promote apoptosis. However, because of the presence of IGFBP proteases, two *in vitro* studies have found that IGFBPs are able to stimulate the growth of cancer cells (17). Our study showed significant correlation for IGFBP-3 expression and HER2 overexpression. Although statistical significance was not obtained, a worse overall survival for IGFBP-3 positive group was noted.

In conclusion, the immunohistochemical expression of IGF-IR and IGFBP-3 suggested that IGF-IR expression is a favorable prognostic factor in breast cancer. In addition, IGF-IR expression is associated with tamoxifen-resistance. Prospective studies for utilization of IGF-IR expression with hormone therapy in primary breast cancer are warranted.

Acknowledgements

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