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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Immunohistochemical evaluation of insulin-like growth factor receptor 1 in breast cancer

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SUMMARY

Introduction/Objective Activation of insulin-like growth factor receptor (IGF-1R) results in cell transition from growth phase to synthesis phase of cell cycle. Breast cancer is categorized into prognostic and therapeutic subtypes based upon hormone receptor, estrogen receptor (ER), and progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER-2) expression.
The objective of this study was to examine the expression of IGF-1R in a specific subtype invasive breast cancer and its correlation with basic histopathological and immunohistochemical prognostic parameters.

Methods Formalin-fixed paraffin-embedded tumor samples were obtained from 129 female patients with invasive breast cancer (I–III disease stage) with the follow-up ranging 36–108 months (average 48 months). For immunohistochemical staining, we used monoclonal antibodies for ER, PR, IGF-1R, and polyclonal antibody for HER-2.

Results IGF-1R inversely correlated with tumor stage ($p = 0.017$), tumor grade ($p = 0.001$), HER-2 ($p = 0.003$), whereas significant positive correlation was found with multifocality/multicentricity of breast cancer ($p = 0.036$), ER ($p = 0.001$) and PR ($p = 0.0001$) expression. Cox-regression analysis for relapse-free survival (RFS) showed that disease stage ($p = 0.039$) and HER-2 ($p = 0.033$) were independent prognostic factors. IGF-1R did not predict clinical outcome in patients with breast cancer ($p = 0.488$, Kaplan–Meier test for RFS).

Conclusion Patients with low stage and grade hormone-dependent breast cancer had a significantly higher IGF-1R expression than patients with triple negative or HER-2 overexpressed cancer. The present findings also highlight that IGF-1R expression in multicentric/multifocal breast cancer supports the key roles in tumor initiation.

Keywords: insulin-like growth factor 1 receptor (IGF-1R); hormone-dependent breast cancer; HER-2

INTRODUCTION

Insulin receptor family represents an activator of class II tyrosine kinase with three members: insulin receptor (IR), insulin-like growth factor receptor 1 (IGF-1R), and insulin-like growth factor receptor 2 (IGF-2R). IR activation influences metabolic activity in vertebrates. IGF-1R activating results in proliferation and differentiation of cells. IGF-2R is structurally and functionally different from the IR and IGF-1R, it is a monomer without tyrosine kinase activity. IGF-1R is a dimmer made of α and β subunits and has the same structure as the IR with which it builds hybrid receptors (IR/IGF-1R) [1, 2, 3]. IRs can be activated by insulin and two insulin-like growth factors (IGFs): insulin-like growth factor 1 (IGF1) and insulin-like growth factor 2 (IGF2). Many cells have been identified as producing as well as responding to the IGFs, including fibroblasts, chondrocytes, osteoblasts, granulosa cells, and epithelial breast cells. In circulation, IGF1 and IGF2 are attached to six insulin-growth binding proteins (IGFBP 1–6) and protected from the action of proteases (Figure 1). IGF-1R together with the hormone receptors regulates the development of the epithelium of the normal glandular breast tissue [4, 5]. Breast cancers are categorized into subtypes based on immunohistochemical hormone receptors expression (ER and PR) and human epidermal growth factor 2 (HER-2) expression. There are two major groups: hormone-dependent/luminal breast cancer involves luminal A (ER+, PR+, HER-2/-, $Ki67^{low}$) and luminal B (ER+, PR+/-, HER-2+/-, $Ki67^{high}$); hormone-independent/basal-like breast cancer involves triple negative (TNBC) breast cancer (ER-, PR-, HER-2-) and HER-2 overexpressed (ER-, PR-, HER-2+). The TNBC subtype does not express therapeutically targetable ER, PR, or HER-2 receptors, making the aggressive subtype difficult to treat [6]. Nowadays, IGF-1R makes an attractive target for investigation for a different type of malignancy and anticancer therapy. The prognostic and predictive role of IGF-1R in breast cancer is still unknown. The optimal cut-point and standardized immunohistochemical expression of this receptor are subjects of discussion [7]. A few studies have examined the relationship of the IGF-1R expression according to the hormone and HER-2 and resistance to antiestrogen therapy [8, 9]. Some *in vitro* studies have

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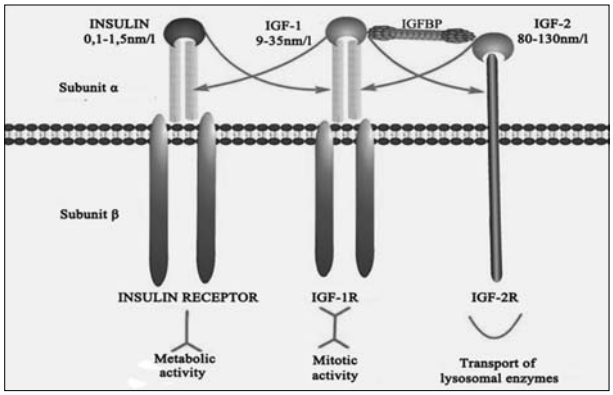

Figure 1. The structure of insulins receptors and concentrations of insulin-like growth factors (IGFs) in the blood; IGFs: insulin, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor 2 (IGF-2); insulin-like growth factor-binding protein (IGPB); insulin receptor (IR); insulin-like growth factor 1 receptor (IGF-1R); insulin-like growth factor 2 receptor (IGF-2R); extracellular subunit of IGF-1R and IR (subunit α); intracellular subunit of IGF-1R and IR (subunit β)

given promising results, supporting the rationale for dual targeting of HER-2 and/or IGF-1R as an improved treatment regimen for advanced therapy tailored to different types of cancer [10].

METHODS

Patient selection

Biopsy specimens for 129 invasive breast cancer in stage I–III diagnosed at the Department of Pathology of the University Hospital Foča (Republic of Srpska) from January 2008 to January 2013 were taken for the study. We retrospectively analyzed the Clinical Centre medical data collected from the Department of Surgery, Department of Oncology, and records of family doctors. The prospective follow-up was 48 months (range 36–108) with last data obtained in November 2016. Subjects did not receive preoperative chemo-/radio- or hormone therapy. Minimum resection margin distance of invasive cancer or *in situ* component was 3 mm. Postoperative therapy for individual subtypes of breast cancer was determined following St Gallen consensus from 2008 [11]. The stage of breast cancer was determined following American Joint Committee on Cancer classification from 2010. Histologic grade of the tumor is determined by Elston–Ellis modification of the Scarff–Bloom–Richardson grading systems [12].

Immunohistochemical staining methods

Formalin-fixed, paraffin-embedded tissue samples were cut at 3–5 μm. Following standard procedure, they were dried (30 minutes in the air), "baked" (60 minutes at 65°C) in an oven, dewaxed in xylene (two changes of five minutes), underwent drop-down rehydration concentrations of ethyl alcohol (100%, 96%, 70%, five minutes for each change), and were rinsed in distilled water. Endogenous peroxidase activity was blocked by 3% H_2O_2 (10 minutes at ambient temperature), and the unmasking of antigens was derived by heat treatment of tissue in a microwave oven. Sections were incubated with primary antibodies: mouse monoclonal anti-IGF-1R (clone 24-31 ab4065, dilution 1:50; Abcam, Cambridge, UK); mouse monoclonal anti-ERα clone 1D5 (M7047, dilution 1:60; DAKO Corporation, Carpinteria, CA, USA); mouse monoclonal anti-PR clone 636 (M3569, dilution 1:100; DAKO Corporation); and polyclonal rabbit anti-HER-2 clone 340 (A0485, dilution 1:60; DAKO Corporation). After washing, primary antibodies were treated with streptavidin peroxidase for 15 minutes. DAB chromogen was added in the final procedure step to visualize a positive. During a short incubation period (± 51 minutes), a pre-formed complex was able to develop a brown colour in the interaction with the DAB chromogen. Following immunohistochemical staining (IHC) of the tissue sample, specimens were stained with Mayer's hematoxylin, dehydrated through a series of ethyl alcohols up to absolute alcohol (70%, 90%, and 100%), washed in xylene and mounted in Biomont. The IGF-1R protein was located at the plasma membrane (α subunit) and the cytoplasm (β subunit). Placental tissue was utilized as an adequate external control. Stainability was estimated semiquantitatively based on Allred scoring system. Summarizing of the percentage of positive tumor cells (< 1% = 1; 1–10% = 2; 11–33% = 3; 33–66% = 4; 67–100% = 5) and staining intensity (1 = weak staining can easily be observed at high-power field; 2 = moderate staining can easily be seen under moderate power objective magnification; and 3 = strong staining can easily be observed under low power objective magnification), the expression was scored as follows: negative (0–2), low 1+ (3–4), moderate 2+ (5–6), and strong 3+ (7–8). Scores of 0 and 1 were considered to be a negative finding, and scores of 2 and 3 a positive one. The same method was applied to ER and PR scoring. Hormone receptor positivity is defined as Allred score of > 2 [13, 14]. For the evaluation of HER-2, only staining of the tumor cell membranes was considered to be specific. Positive cases were defined as IHC-3+ and IHC-2+ FISH retested with amplification ratio C > 2.0 [15].

Statistical analysis

The association between the intensity of expression with tumor grade, lymph node status, and tumor size was studied with linear correlation method based on the Pearson correlation coefficient (r). For relapse-free survival (RFS) we used the Kaplan–Meier test, while the Cox proportional hazard regression model was used for multivariate analysis. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was established at the $p < 0.05$ level.

RESULTS

Characteristics (clinical and histopathological data) of 129 patients with breast cancer are shown in Table 1. One hundred

Table 1. Clinical, histopathological, and immunohistochemical data of 129 patients with breast cancer

Variable	n (%)
Median age (range)	59 (33–84)
Menopausal status	
no	24 (18.6)
yes	105 (81.4)
Tumor stage	
I	10 (7.8)
II	56 (43.4)
III	63 (48.8)
Tumor type	
ductal	71 (55)
lobular	32 (24.8)
other	26 (20.2)
Tumor size	
< 2 cm	16 (12.4)
2–5 cm	75 (58.1)
> 5 cm and inflammatory carcinoma	38 (29.5)
Lymph node metastasis	
node negative	40 (31)
1–3 node positive	37 (28.7)
4–9	32 (24.8)
> 10	20 (15.5)
Postoperative therapy	
tamoxifen	97 (75)
chemotherapy	89 (69)
chemotherapy + Herceptin	33 (25.6)
radiotherapy	99 (76.8)
Estrogen receptor	
0	32 (24.8)
1	13 (10.1)
2	16 (12.4)
3	68 (52.7)
Progesterone receptor	
0	53 (41)
1	13 (10)
2	22 (17.2)
3	41 (31.8)
HER-2	
negative case*	96 (74.4)
positive case**	33 (25.6)

*Immunohistochemical expression 0, 1, and 2 with FISH retested negative; **immunohistochemical expression 3 and 2 with FISH retested positive (amplification ratio C > 2.0)

seventeen patients (90.7%) were alive without evidenced progression of the disease; 12 patients (9.3%) had a relapse of the disease. Bone metastases were registered in five (41.7%) patients, locoregional recurrence in two (16.7%), and one patient (8.3%) had metastases in lungs, liver, brain, remote lymph node and in two organ systems.

IGF-1R expression

Forty-seven of the 129 samples (37.2%) of breast cancer showed no or weak staining (scores of 0 and 1+), 41 (31.8%) moderate (score of 2+) and 42 (32.6%) strong immunohistochemical expression (score of 3+) (Figure 2).

Table 2. Multivariate Cox proportional hazards regression analysis for RFS in breast cancer patients

Variable	B	SE	HR	p-value	95% CI
Disease stage	4.8068	2.3302	122.344	0.0391	1.3008–11506.4
Lymph node stage (pN)	-0.1966	0.3923	0.8216	0.16164	0.3823–1.765
HER-2	1.3284	0.6259	3.7748	0.00338	1.1140–12.7915
IGF-1R	0.2511	0.2930	1.2854	0.3914	0.7260–2.2758

B – beta coefficient; SE – standard error; HR – hazard ratio; CI – confidence interval; HER-2 – human epidermal growth factor receptor 2; IGF-1R – insulin-like growth factor 1 receptor

Table 3. Correlation of insulin-like growth factor 1 receptor expression and prognostic parameters in breast cancer

n = 129	95% CI	r	p-value
Disease stage	-0.3671 to -0.0372	-0.2081	0.0175
Tumor size	0.1782 to 0.1661	-0.006221	0.9440
Lymph node stage (pN)	-0.319 to 0.162	-0.1564	0.075
Tumor grade	-0.492 to-0.189	-0.3501	0.0001
Lymphatic invasion (L1)	-0.249 to 0.092	-0.0812	0.3584
Venous invasion (V1)	-0.127 to 0.216	0.04615	0.602
Menopausal status	-0.211 to 0.132	-0.04105	0.642
Multifocal/multicentric cancer growth	0.011 to 0.344	0.1832	0.036
Age	-0.166 to 0.178	0.006337	0.943
ER	0.397 to 0.645	0.5328	0.0001
PR	0.331 to 0.598	0.4754	0.0001
HER-2	-0.410 to -0.088	-0.2567	0.003

r – Pearson correlation coefficient; ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2

Neither IGF-1R, ER, nor PR were significant predictors of RFS (p = 0.48, p = 0.26, p = 0.28, respectively; Kaplan–Meier test). We confirmed the prognostic value of tumor stage, lymph node metastasis, and HER-2 expression (Figure 3) Disease stage and HER-2 expression were of prognostic significance on relapse-free survival (RFS) in the final Cox proportional hazard multivariate analysis (Table 2).

Correlation among expression of IGF-1R and ER, PR, and HER-2

IGF-1R was positively associated with ER (p = 0.001), PR (p = 0.001), and multifocality/multicentricity of breast cancer (p = 0.039). Inverse correlation existed between IGF-1R and disease stage (p = 0.017), tumor grade (p = 0.0001), and HER-2 (p = 0.003) expression. Other parameters did not show statistically significant correlation with IGF-1R (Table 3).

DISCUSSION

Up to now, the prognostic value of the IGF-1R expression on disease outcome has been controversial, with studies reporting both positive and negative findings [16, 17, 18]. In our study, IGF-1R expression did not independently predict on relapse-free survival and clinical outcome. Conflicting results may arise from discordant methodological

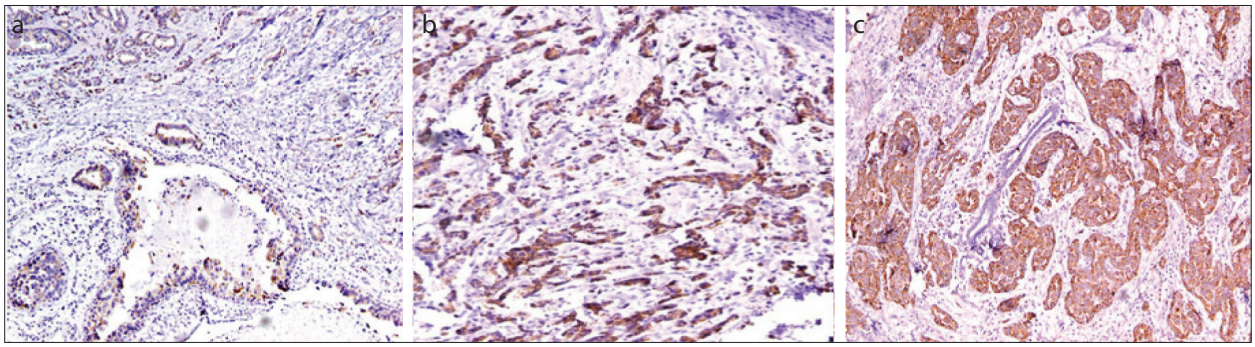

Figure 2. Immunohistochemical expression of insulin-like growth factor 1 receptor in breast cancer (formalin-fixed paraffin-embedded sections, ×40); the expression was scored according to area and intensity of membranous or citoplasmatic staining: a) score 1+; b) score 2+; c) score 3+

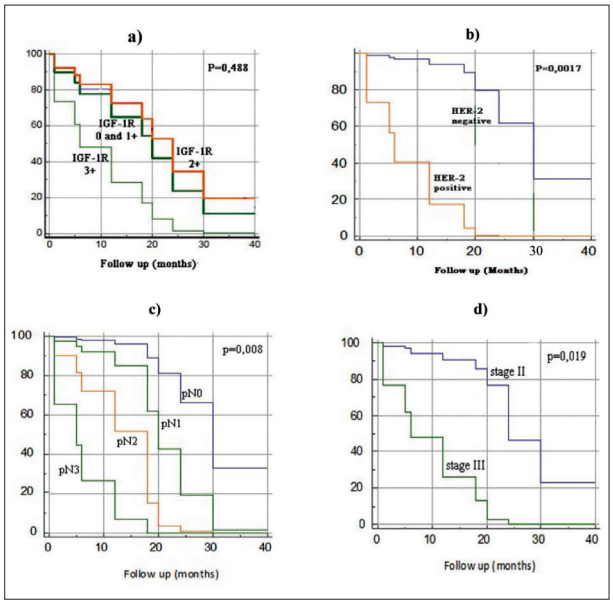

Figure 3. Relapse-free survival analysis (Kaplan–Meier test) prognostic value of a) insulin-like growth factor 1 receptor (IGF-1R), b) human epidermal growth factor receptor 2, c) lymph node metastases, and d) disease stage

approaches, distinct molecular subtypes studied, genetic differences between different populations, and tumor heterogeneity. Our study demonstrated high expression (score of 2+ or 3+) of IGF-1R in 64.4% of the samples. This is in line with some other studies [19]. Up to 50% of breast tumors express the activated form of IGF-1R. In our study, IGF-1R was predominantly expressed in well-differentiated and hormone-dependent breast cancers. IGF-1R and the ER are critical for mammary gland development. The ER and the IGF pathway show dynamic and intricate interference, resulting in bidirectional regulation of expression and activity. ER transcriptionally upregulates IGF-1R expression. Positive correlation exists between cyclin D1 and ER expression, which has already been explained in both experimental and clinical studies, because ER acts as the main mitogen stimulator in breast cancer [20]. The role of IGF-1R in mammary stem cell maintenance and a necessity for lineage differentiation suggest that aberrantly expressed IGF-1R may be capable of enhancing cell potential and changing cell fate in a tumor, perhaps even in tumors composed of fully differentiated cells. As discussed above, the IGF-1R expression is essential for driving luminal alveolar differentiation, linking IGF-1R to the luminal lineage [21, 22]. Furthermore, many studies indicate a down-regulation of IGF-1R upon cancer progression, whereas others report elevated levels in metastatic stages. Once cancer has been confirmed, the importance of IGF-1R for disease progression remains unclear. In our study, IGF-1R was highly expressed in patients with early breast cancer and overall positively associated with good prognostic variables. We have indicated the decrease of IGF-1R expression with disease progression. High-level IGF-1R expression had low stage breast cancer with multiple/multicentric unilateral or bilateral growth. We emphasize that IGF-1R could have effects in early phases of development of luminal breast cancer. Numerous in vitro studies demonstrate IGF-1R as a driver of self-renewal, stem cell surface markers, migration, and invasion in both normal and cancerous tissues and tumor initiation in hepatic, lung, prostate, and breast cancers [23]. Approximately 40–60% of ER-positive tumors express IGF-1R, while expression in ER-negative tumors is only 10–20%. Considering the correlation of IGF-1R with hormone-dependent tumor type and early stage, we assume that ER/IGF-1R axis might represent a distinct proliferative pathway during breast cancer development. Other studies report that IGF-1R is a receptor expressed in the basaloid type breast cancer and has a role in anti-HER-2 resistance (Herceptin) [24]. We found a negative correlation between IGF-1R-overexpressed and HER-2-positive breast cancer. In general, IGF-1R correlates with good prognostic markers, such as ER and PR-positivity and HER-2-negativity. However, the IGF-1R expression has differential effects in different breast cancer subtypes. For example, its expression has been shown to be positively correlated with improved breast cancer-specific survival among patients with ER-positive tumors, while its expression was associated with an inferior prognosis in patients with HER2-overexpressing or triple-negative tumors. In models of breast cancer cells that overexpress HER-2, anti-HER-2 activity is disrupted by increased expression of IGF-1R. Nowadays, antibody-based molecular therapies have been developed for HER-2. IGF-1R can form heterodimers with the HER-2 tyrosine kinase and contribute to the development of resistance to HER-2 inhibition with the monoclonal antibody. An association between IGF-1R and HER-2 in IGF-1R-dependent

tumor transformation has been reported in mammary luminal epithelial cells, indicating that the IGF-1/HER-2 cross-talk may occur via autocrine and paracrine signaling. A recent study concluded that neoadjuvant therapy can induce changes in the IGF-1R expression. Therefore, there are many studies with opposite results [25, 26]. It is possible that IGF-1R expression is dependent not only on the specific cell type and disease stage, but also it is dependent on specific therapy and another factor. In some other tumors, like lung cancer, the expression of IGF-1R correlated with a less favorable outcome [27]. This indicates that IGF-1R activities might be not only diverse but also tissue-specific. To test this hypothesis, we evaluated the protein expression of the most important components of the IGF-1R signaling pathway in hormone-dependent breast cancer and their significance according to the tumor subtypes. This clearly indicates other functions of IGF-1R that are not related to cell cycle progression and tumor aggressiveness, which may include cell differentiation and growth arrest.

CONCLUSION

IGF-1R is particularly important for the establishment and maintenance of the transformed phenotype and for the survival of tumor cells with anchorage-independent growth in breast carcinoma with luminal differentiation.

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Процена имунохистохемијске експресије рецептора инсулину-сличног фактора раста 1 у карциному дојке

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САЖЕТАК

Увод/Циљ Активација рецептора инсулину-сличног фактора раста 1 (*IGF-1R*) изазива покретање ћелијског циклуса из фазе раста (*G*1) у фазу синтезе (*S*). Оболели од карцинома дојке се деле на специфичне терапијске и прогностичке групе у зависности од експресије хормонских рецептора, естрогених (*ER*) и прогестеронских (*PR*), и експресије рецептора хуманог епидермалног фактора раста 2 (*HER*-2).
Циљ рада је откривање степена експресије *IGF-1R* у туморском ткиву код одређених терапијских група оболелих од карцинома дојке и његова корелација са важећим патохистолошким и имунохистохемијским прогностичким параметрима.

Методе Истраживање је спроведено на 129 укалупљених узорака инвазивног карцинома дојке код жена (у стадијуму болести I–III) уз постоперативно праћење тока болести 48 (36–108) месеци. За имунохистохемијско бојење коришћена су моноклонска антитела за визуализацију: *ER*, *PR*, *IGF-1R* и поликлонално антитело за *HER*-2.

Резултати Експресија *IGF-1R* је била у негативној корелацији са стадијумом болести ($p = 0,017$), степеном диферентованости тумора ($p = 0,001$) и експресијом *HER*-2 ($p = 0,003$). Позитивна корелација овог рецептора налазила се између мултифокалног/мултицентричног макроскопског начина раста карцинома дојке ($p = 0,036$) и експресије *ER* ($p = 0,001$) и *PR* ($p = 0,0001$). Коксова регресиона анализа времена без прогресије болести (*RFS*) показала је да стадијум болести ($p = 0,039$) и *HER*-2 ($p = 0,033$) представљају независне прогностичке варијабле. Експресија *IGF-1R* није имала утицај на клинички ток болести код особа са раком дојке ($p = 0,488$, Каплан–Мајер тест за *RFS*).

Закључак Болесници оперисани у почетном стадијуму болести са дијагностикованим добро диференtованим, хормонски зависним раком дојке имају већу *IGF-1R* експресију у односу на болеснике са троструко негативним и *HER*-2 амплификованим туморима дојке. Повећана *IGF-1R* експресија код карцинома са мултифокалним/мултицентричним макроскопским начином раста указује на значајну улогу овог рецептора у фази настанка тумора.

Кључне речи: рецептор инсулину-сличног фактора раста 1 (*IGF-1R*); хормонски зависни рак дојке; *HER*-2