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The immunoexpression of EGFR, HER2 and HER3 in malignant serous ovarian tumors

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Abstract

The expression of epidermal growth factor (EGF) receptors is common in human carcinomas and the proteins are used as therapeutics targets. In this study, we analyzed the immunoexpression of EGFR, HER2 (EGFR2) and HER3 (EGFR3) in 41 cases of serous borderline ovarian tumors and carcinomas, in relation to the degree of differentiation and tumor stage. The quantification of the results was done using the final staining score (FSS), which took into account the number of labeled cells and the intensity of immunoreactions. For all the receptors, the FSS values corresponding to the high-grade serous carcinomas were significantly superior compared with low-grade carcinomas and borderline tumors. Also, the FSS values associated with advanced stages ovarian tumors were significantly superior compared to those in the initial stages. In this study, we found positive linear correlations between the values associated with the expression of EGF receptors. The relation of EGFR, HER2 and HER3 immunoexpression with the lesion subtype, tumor grade and stage, designates the EGF receptors system as possible therapeutic target in ovarian serous tumors.

Keywords: ovarian serous tumors, EGFR, HER2, HER3.

Introduction

For several years, the efforts to identify the prognostic factors of ovarian carcinomas were focused on molecular markers that were most often investigated by immunohistochemistry. Although the large number of the potential markers candidates as prognostic factors is remarkable, none has yet been approved for clinical use.

The ErbB family of tyrosine kinase receptors plays a role in the tumorigenesis of several types of solid tumors, and includes the epidermal growth factor (EGF) receptors – EGFR (HER1, ErbB1), EGFR2 (HER2/neu, ErbB2), EGFR3 (HER3, ErbB3) and EGFR4 (HER4, ErbB4) [1]. The abnormal activation of these receptors has been associated with various pathological processes including cellular transformation [2], the four EGF receptors having key role in promoting carcinogenesis through proliferation, survival, migration, adhesion and cellular differentiation disruption.

With the aim of contributing to a better understanding of ovarian carcinogenesis and the selection of reliable prognostic markers, we studied the immunohistochemical expression of a series of markers that addresses to cell growth regulation, represented by EGFR, HER2 and HER3.

Materials and Methods

This study included a total of 41 cases of serous carcinomas and serous borderline tumors from the Clinics of Gynecology and Surgery, Emergency County Hospital, Craiova, Romania. The surgical excision specimens were fixed in 10% buffered formalin, processed by the paraffin-embedding technique and Hematoxylin–Eosin staining. The classification of the lesions was done according to the literature recommendations [3].

Subsequently, serial sections were performed, which have undergone the immunohistochemical processing using Biotin-Free Catalyzed Amplification System (CSA) II (Dako, Redox, Romania, code K197), in the case of EGFR and HER3, and Labeled Streptavidin–Biotin (LSAB)+ System–Horseradish Peroxidase (HRP) (Dako, Redox, Romania, code K0675) for HER2/neu. For the visualization of the reactions, 3,3'-diaminobenzidine (DAB) (Dako, code K3468) was used, and for the validation of the reactions, positive and negative external controls were used (by omitting the primary antibody) (Table 1).

Table 1 – *Antibodies used panel*

Antibody	Clone / Manufacturer	Dilution	Antigen retrieval	External positive control
EGFR	H11 / Dako	1:300	–	Placenta
HER2/neu (EGFR2)	Polyclonal / Dako	1:75	Citrate buffer, pH 6	Breast cancer
HER3 (EGFR3)	DAK-H3-IC / Dako	1:100	Tris-EDTA buffer, pH 9	Colon

EGFR: Epidermal growth factor receptor; EDTA: Ethylenediamine-tetraacetic acid.

We assessed the semi-quantitative expression of EGFR, HER2 and HER3, through a scoring system that was assigned independently by two specialists, based on the

staining intensity and the percentage of labeled cells. The intensity score was noted as 1 (low intensity), 2 (moderate) and 3 (high intensity). The score of the percentage labeled cells was noted as 1 (5–25% positive cells), 2 (26–50% positive cells), 3 (51–75% positive cells) and 4 (>75% positive cells), the threshold for the positive reactions being 5%. The multiplying of the intensity and percentage scores allowed the calculation of the final staining score (FSS), with values between 1–12.

For the statistical analysis, a final staining score was regarded as low expression for the values between 1–4, and a final staining score of 6–12 corresponded to the group with high expression, the analysis being performed using χ^2 (*chi*)-square and Pearson's tests within the automated software Statistical Package for the Social Sciences (SPSS) 10. The *p*-values less than 0.05 were considered significant.

The local Ethical Committee approved the study and the written informed consents were obtained from the patients.

Results

Histopathological analysis of the 41 selected cases revealed in 14 cases serous borderline tumors (SBTs) and serous carcinomas in 27 cases, of which three low-grade serous carcinomas (LGSCs) and 24 cases of high-grade serous carcinomas (HGSCs). The tumors corresponded to the stage I of disease in 14 cases, stage II in three cases and stage III in 24 cases.

The analysis of the EGFR, HER2 and HER3 immunostaining indicated the presence of signals both in tumor cells and stromal elements. The study of EGFR immunoexpression for the 41 cases of serous borderline ovarian tumors and carcinomas, indicated the positivity of the reaction in 24 (58.5%) cases, allocated in all groups of analyzed tumors, but in a limited number of SBTs compared to carcinomas, respectively in three cases and in 21 cases. As regards the FSS of the serous analyzed tumors, we found that the highest mean values were in HGSCs, respectively 9.5, compared with LGSCs and SBTs, in which the mean values was 1.66 in the both cases.

Table 2 – ***The distribution of positive tumors in relation with the mean FSS values and tumor stage***

Tumor type / markers		Stage No. of cases/FSS mean value		
		Stage I	***Stage II***	***Stage III***
EGFR	SBT	3/1.66		
	LGSC	2/2	1/1	
	HGSC		8/9	10/10.1
HER2	SBT	3/1.33		
	LGSC	1/2		
	HGSC		6/4.6	7/9
HER3	SBT	8/1.2		
	LGSC	1/4		
	HGSC		7/7	9/7.3

FSS: Final staining score; EGFR: Epidermal growth factor receptor; SBT: Serous borderline tumor; LGSC: Low-grade serous carcinoma; HGSC: High-grade serous carcinoma.

We noticed the presence of EGFR immunostaining in all analyzed groups, with cytoplasmic and membrane expression, sometimes with evident granular cytoplasmic pattern.

In SBTs, EGFR was expressed in 20.6±10 cells, with low or moderate intensity (Figure 1A), similar aspects being present in LGSCs, in which the mean value of labeled cells was 16.6±6.1 (Figure 1B). These tumors corresponded to the disease stages I and II. By contrary, in HGSCs we noticed an immunostaining with diffuse and with increased intensity in all positive cases for this marker, the mean number of labeled cells being 69±13.6 (Figure 1C). The tumors corresponded to the stage II and respectively stage III of disease.

The analysis of HER2 expression indicated the reaction positivity in 17 (41.5%) cases, with a small number of SBTs compared to carcinomas, respectively in three *versus* 14 cases. The immunostaining was observed in membrane, but also cytoplasmic apical.

The FSS mean values analysis for the serous tumors revealed higher values for HGSCs, respectively 7, similar with the results observed in case of EGFR. For SBTs and LGSCs, the FSS mean values were 1.3 and respectively 2.

In SBTs, HER2 was expressed in 28.3±10.4 of cells with low or moderate intensity (Figure 1D). In the HER2-positive LGSCs, the number of labeled cells was 45%, with low intensity of reaction (Figure 1E). In contrast, in HGSCs we observed diffuse immunostaining and predominantly moderate or increased intensity in 62±15.4 of cells (Figure 1F).

The analysis of HER3 immunoexpression revealed cytoplasmic and membrane positivity in 25 (60.9%) cases, allocated to all tumor groups. We observed the HER3 positivity in a small number of SBTs compared to carcinomas, respectively in eight and in 17 cases.

The mean values of FSS were highest in HGSCs, respectively 7.1, similar with the results observed for EGFR and HER2. The FSS mean values for SBTs and LGSCs were lower, respectively 1.2 and 4.

In SBTs lesions, HER3 was expressed in 15±6.1 cells, predominantly with low intensity (Figure 1G). In the HER3-positive LGSCs, the number of labeled cells was 40%, the intensity of reaction being moderate (Figure 1H). In HGSCs, the immunostaining was diffuse with moderate or high intensity in all analyzed cases, the mean number of labeled cells being 60±13.7 (Figure 1I).

The statistical analysis of the mean FSS values in relation to the tumor type indicated significantly higher values in HGSCs compared with LGSCs and SBTs, both for EGFR ($p<0.0001$, *chi*-square test), HER2 ($p=0.024$, *chi*-square test) and HER3 ($p=0.002$, *chi*-square test) (Figure 2, A–C).

Also, the analysis of the mean FSS values in relation to tumor stage indicated values significantly higher in stages II and III lesions *versus* stage I tumors, aspect which was observed for each of the analyzed markers ($p<0.05$, *chi*-square test). Analyzing the distribution of mean percentage values of EGF receptors indicated positive linear correlations between EGFR/HER2 ($p=0.001$, Pearson's test), EGFR/HER3 ($p<0.001$, Pearson's test) and HER2/HER3 ($p=0.001$, Pearson's test) (Figure 2D).

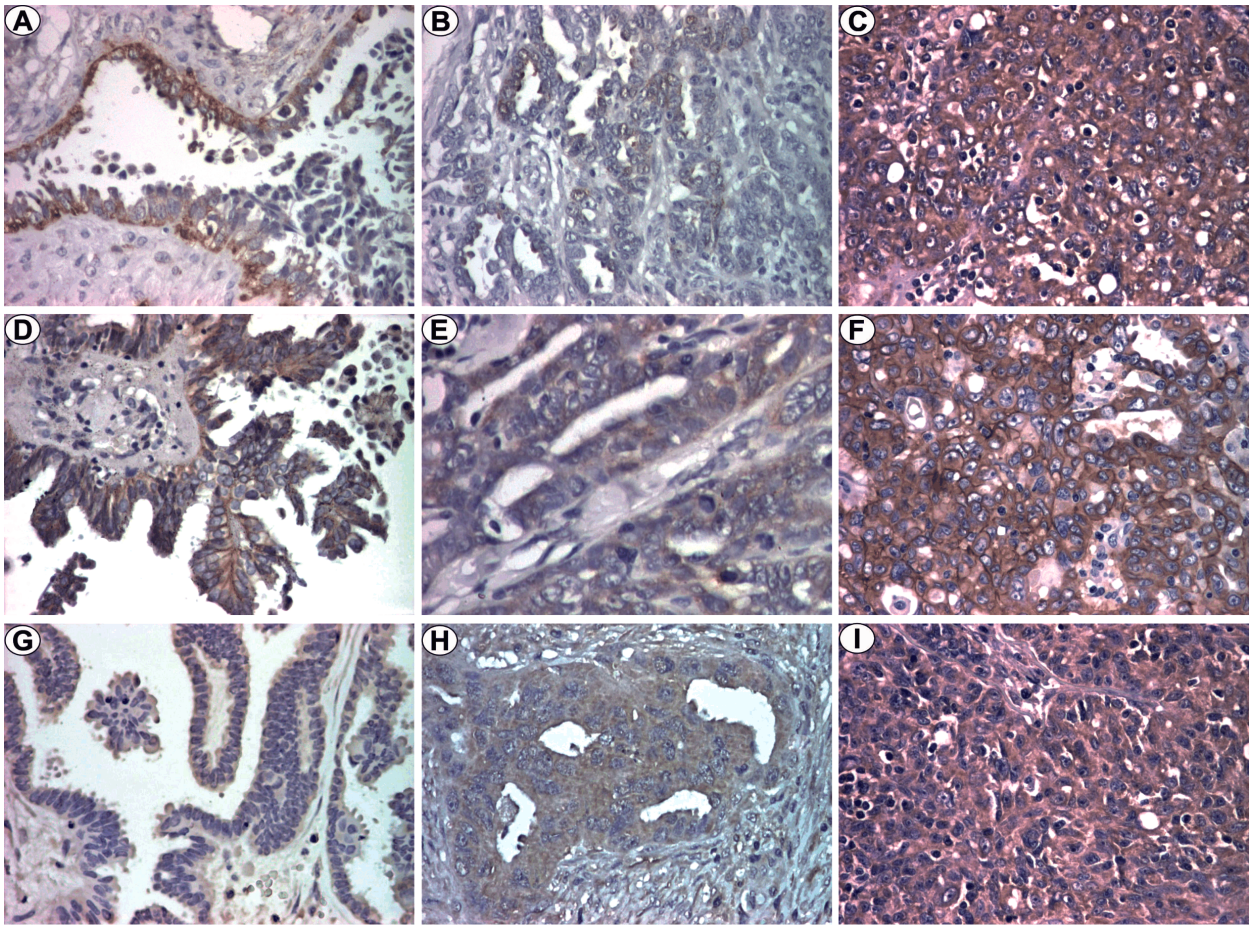

Figure 1 – ***(A, D and G) SBT; (B, E and H) LGSC; (C, F and I) HGSC. EGFR immunostaining: (A–C) ×200; HER2 immunostaining: (D–F) ×200; HER3 immunostaining: (G–I) ×200. SBT: Serous borderline tumor; LGSC: Low-grade serous carcinoma; HGSC: High-grade serous carcinoma; EGFR: Epidermal growth factor receptor.***

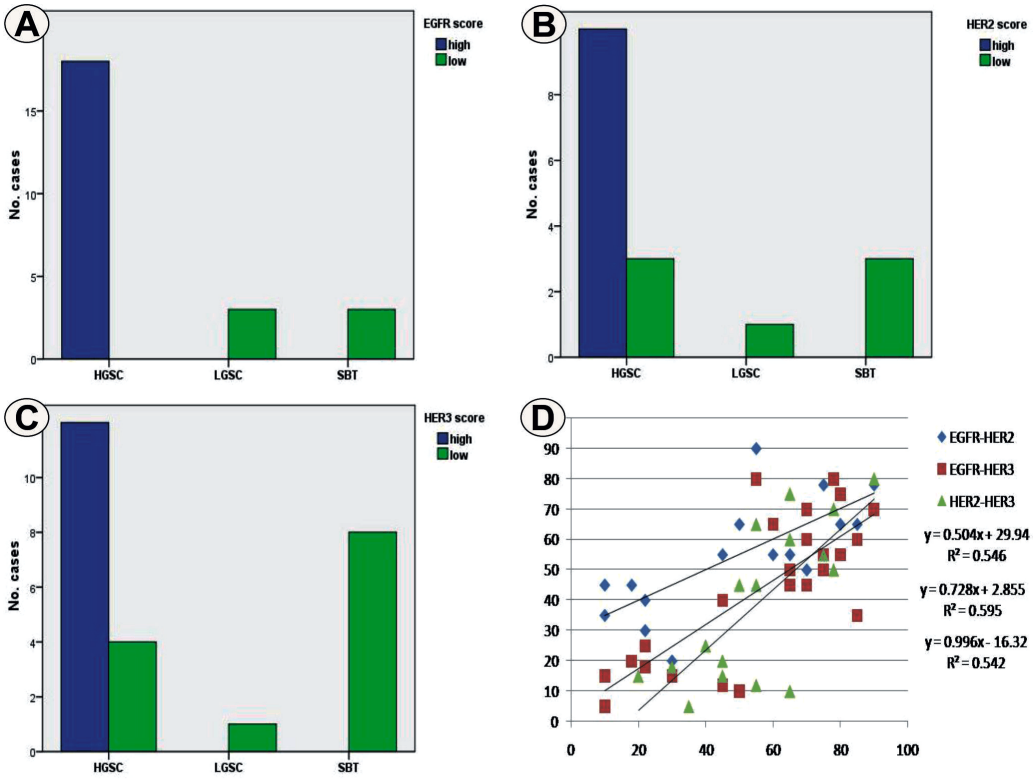

Figure 2 – ***(A–C) EGFR, HER2, HER3 scores distribution depending on tumoral subtypes; (D) The distribution of labeled cells mean values for EGFR, HER2 and HER3. EGFR: Epidermal growth factor receptor; HGSC: High-grade serous carcinoma; LGSC: Low-grade serous carcinoma; SBT: Serous borderline tumor.***

Discussion

The coexpression of different ErbB receptors and the EGF-like growth factors is a common phenomenon in human carcinomas, suggesting that the growth and survival of tumor cells is supported by a network of receptors/ligands of the ErbB family [4]. That suggests that in this way could also affect the tumor response to targeted therapeutic agents against the receptor/ligand ErbB system.

In this study, we observed the EGFR expression in both malignant serous borderline and carcinomas tumors, with various incidents, respectively three (21.4%) cases and 21 (77.7%) cases. There are relatively few studies that have examined the expression of EGFR in serous borderline tumors. One study reported the expression of the protein in a significantly higher proportion in carcinomas than in borderline tumors, respectively 69% compared to 18% [5]. In contrast, in ovarian serous carcinomas, the EGFR expression is more common. A large study that included 783 patients reported the overexpression of EGFR in 62% of tumors [6]. In addition, Stadlmann *et al.* observed significant association between amplification and immunohistochemical overexpression of the EGFR protein in serous carcinomas [7].

The statistical analysis the EGFR expression indicated significantly higher values in high-grade and advanced stages carcinomas. In literature, the significance of the EGFR immunoexpression on malignant serous ovarian tumors is controversial [8]. Although it has not been demonstrated the EGFR expression constant correlation with the aggressiveness of the disease, it appears to be associated with poor prognosis and a weaker therapeutic response [9–11].

HER2 protooncogene is involved in the development of many types of human cancer and is extensively evaluated as therapeutic target [2, 4]. Most recent studies using validated techniques in breast cancer, suggest that the overexpression and common amplification of the HER2 in ovarian cancer is actually a fairly rare event [12].

In this study, we observed the HER2 expression in both serous borderline tumors and carcinomas with various incidents, respectively three (21.4%) cases and 14 (51.8%) cases.

Wang *et al.* indicates the positivity for HER2/neu and negativity for the EGFR in borderline and benign ovarian tumors [13], other studies reporting positivity for EGFR and HER2/neu in most borderline tumors; HER2/neu is expressed in 50% of them without being a marker of malignancy [5].

The percentage of patients with HER2/neu positive ovarian cancer differs considerably in various individual studies between 8% and 66% [14–21]. Karaferic *et al.* reports the positivity of HER2/neu in 13.9% of cases, but without the overexpression [22]. In a large study, which included 320 cases of ovarian carcinomas, the overexpression of HER2 (2+/3+) was identified in 13% of cases [23]. Also, according to studies elaborated by Smith *et al.*, the ovarian carcinomas demonstrated the HER2/neu overexpression [24]. By contrary, the Nofech-Mozes S *et al.* have not identified any cases of malignant serous ovarian tumor that overexpressing HER2/neu [25].

In this study, the statistical analysis of HER2 expression indicated significantly higher values in the high-grade carcinomas and advanced stages tumors. For the ovarian cancer, the influence of HER2/neu on prognosis is still debated, since the HER2/neu positive rate of patient varies considerably, the ability of drugs available for HER2/neu therapeutic path being insufficiently explored. Raspollini *et al.* noted the amplification HER2/neu in all 3+ cases, suggesting the therapeutic potential of the gene [26].

In some studies, HER2 overexpression was associated with poor prognosis. It is estimated that HER2/neu oncogene expression may be important in advanced ovarian cancer prognosis [27, 28], but its role in the initial stages of disease has not been established [28].

ErbB3 was considered a "dead" kinase receptor [29] because it does not have significant intrinsic kinase activity [30]. Therefore, in order to induce cell signaling ErbB3 must be phosphorylated by its interactive partners, erbB2 being the most important [31].

In our study, we observed HER3 expression in both serous borderline tumors and carcinomas with various incidents, respectively 57.1% and 62.9%. Also, HER3 values were significantly superior in high-grade advanced and in stages carcinomas.

HER3 overexpression was observed in 53.4% of ovarian cancer patients [32]. A study on the role of C-erbB family in ovarian cancer reported positivity rates of C-erbB2, C-erbB3, and C-erbB4 of 75.5%, 69.3% and respectively 65.3% [33]. Other studies communicate very different results, respectively of only 3% of the analyzed cases [18].

HER3 is overexpressed in ovarian cancer [34] and may represent a new prognostic factor in epithelial ovarian cancer associated with reduced survival, independently of clinical prognostic factors [*The International Federation of Gynecology and Obstetrics* (FIGO) stage, grade and histological type, residual tumor after surgery, age] [32]. In addition, the authors indicate a higher fraction of patients who overexpress HER3 (53.4%), compared with HER2 overexpression (4.9%), highlighting the relevance of HER3 as a possible therapeutic target in ovarian cancer [32]. Other studies indicate conflicting results, reporting a small number of tumors with immunostaining for HER1, HER2 or HER3, indicating that few patients with ovarian cancer have tumors that would benefit from specifically therapy targeted against these receptors [18].

Conclusions

The analysis of the investigated ErbB receptors in malignant serous ovarian tumors indicated their co-expression in both tumor subtypes. HER2 had the lowest incidence, regardless of lesion subtype. The EGFR, HER2 and HER3 immunoexpression relation with lesion subtype, tumor stage and grade, as well as the correlations between the receptors, argue the existence in serous ovarian tumors of an EGF signaling interconnected system, which can be investigated as a possible therapeutic target.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper. All authors read and approved the final manuscript.

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