Opposed roles of follicle-stimulating hormone and luteinizing hormone receptors in ovarian cancer survival

Sir: As ovaries are the target organs of gonadotropins, a relationship with the development or growth of ovarian cancer has been postulated.[1] However, there are few data, obtained with small patient numbers, for follicle-stimulating hormone (FSH) receptor (FSH-R) and luteinizing hormone (LH) receptor (LH-R) expression in ovarian cancer tissue, and hardly any data on their prognostic relevance. Therefore, we conducted this study to quantify LH-R and FSH-R expression in ovarian cancer tissue and to analyse their impact on relapse and survival.

Immunohistochemical (IHC) staining was performed for LH-R and FSH-R expression in 156 ovarian cancer tissue samples. Most patients presented with advanced

Table 1. Patient characteristics

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Patients (*n*)	156
Age at primary diagnosis (a) [years (range)]	58 (18–88)
Histology (%)	
Serous	70.5
Mucinous	13.5
Endometrioid	7.7
Clear cell	8.3
Tumour grading (%)	
Low grade	27.2
Intermediate	36.5
High grade	36.3
Tumor stage (FIGO) (%)	
I	22.6
II	5.8
III	70.3
IV	1.3
Median follow-up time (a) [years (range)]	7.3 (0.3–16.8)
Median relapse-free survival (a) [years (range)]	2.1 (0.9–7.2)
Median overall survival (a) [years (range)]	5.9 (0.3–16.6)
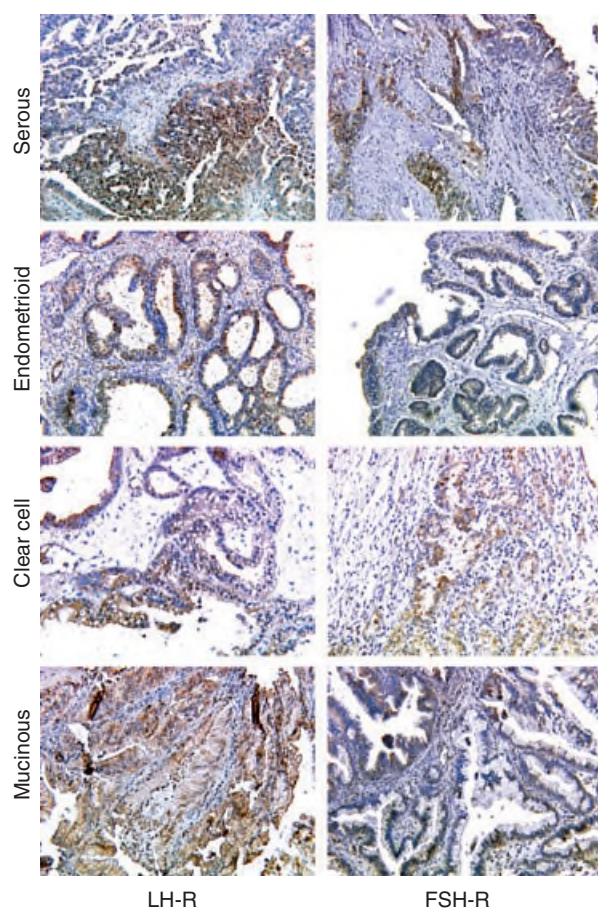
Figure 1. Representative slides of immunohistochemical staining for the luteinizing hormone receptor (LH-R) and follicle-stimulating hormone receptor (FSH-R) for serous, endometrioid, clear cell and mucinous ovarian cancer. No FSH-R or LH-R immunoreactivity was detected in tumour stroma (magnification ×20).

Table 2. Follicle-stimulating hormone receptor (FSH-R) and luteinizing hormone receptor (LH-R) staining in relation to FIGO stage, nodal status, grading and histological subtype

	FSH-R		LH-R	
	Negative [n (%)]	Positive [n (%)]	Negative [n (%)]	Positive [n (%)]
FIGO				
I	13 (37.1)	22 (62.9)	11 (31.4)	24 (68.6)
II	1 (11.1)	8 (88.9)	5 (55.6)	4 (44.4)
III	42 (38.5)	67 (61.5)	39 (35.8)	70 (64.2)
IV	0 (0)	2 (100.0)	0 (0)	2 (100.0)
Nodal status				
Negative	17 (39.5)	26 (60.5)	15 (34.9)	28 (65.1)
Positive	19 (36.5)	33 (63.5)	13 (25.0)	39 (75.0)
Grading				
Low	16 (41.0)	23 (59.0)	15 (38.5)	24 (61.5)
Intermediate	18 (33.3)	36 (66.7)	15 (27.8)	39 (72.2)
High	17 (32.1)	36 (67.9)	25 (47.2)	28 (52.8)
Histological subtype				
Serous	39 (35.5)	71 (64.5)	42 (38.2)	68 (61.8)
Endometrioid	8 (38.1)	13 (61.9)	5 (23.8)	16 (76.2)
Mucinous	5 (41.7)	7 (58.3)	3 (25.0)	9 (75.0)
Clear cell	5 (38.5)	8 (61.5)	5 (38.5)	8 (61.5)

Table 3. Correlation analysis for follicle-stimulating hormone receptor (FSH-R) and luteinizing hormone receptor (LH-R) for FIGO, nodal status, grading and histological subtype

	Nodal status	FIGO	Grading	Histological subtype	LH-R	FSH-R
LHR						
Correlation coefficient	0.108	0.012	−0.091	−0.081	1.000	0.220**
Sigma (two-sided)	0.289	0.885	0.274	0.314		0.006
N	95	155	146	156	156	156
FSH-R						
Correlation coefficient	0.031	−0.024	0.069	−0.035	0.220**	1.000
Sigma (two-sided)	0.767	0.767	0.405	0.663	0.006	
N	95	155	146	156	156	156

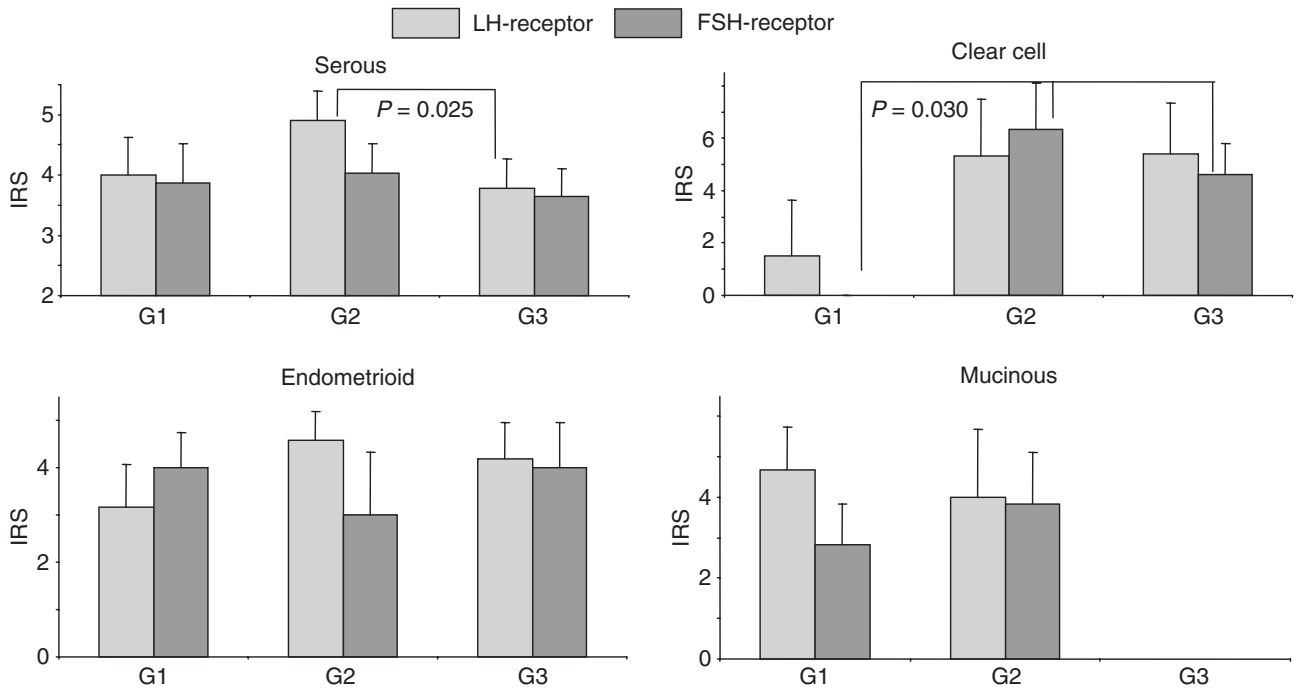**The two-sided correlation is significant with $P < 0.01$ (Spearman rho).

Figure 2. Luteinizing hormone receptor (LH-R) and follicle-stimulating hormone receptor (FSH-R) expression in low-grade (G1), intermediate (G2) and high-grade (G3) tumours of different histological subtypes.
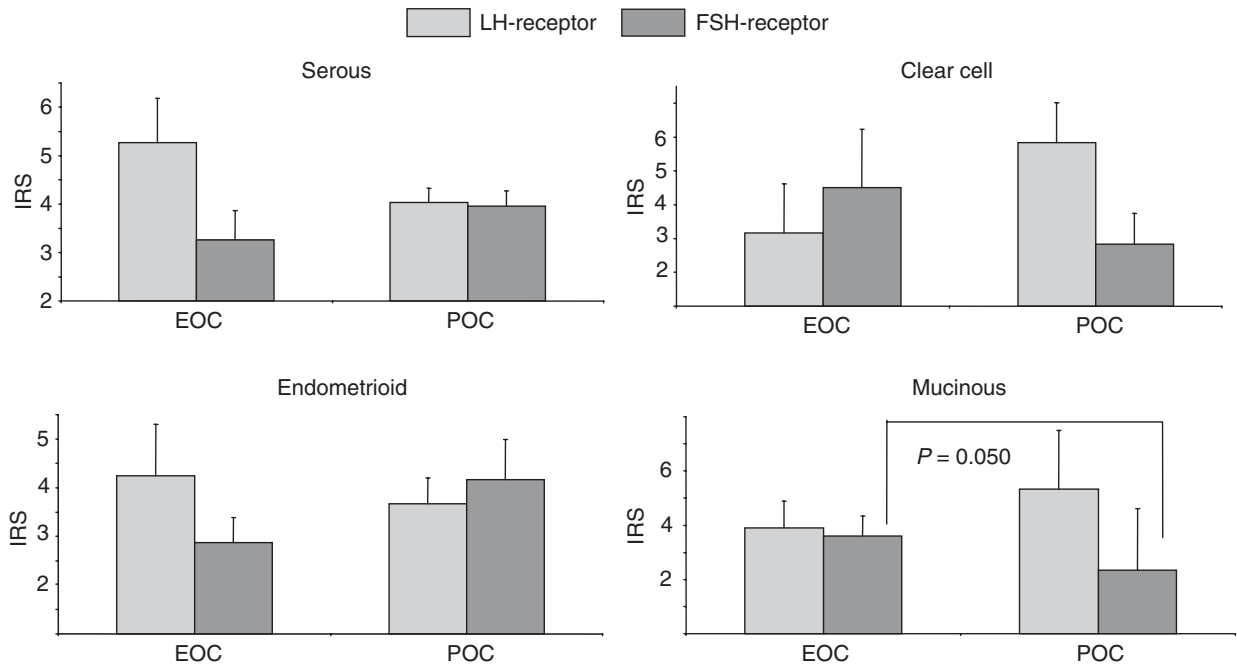

Figure 3. Luteinizing hormone receptor (LH-R) and follicle-stimulating hormone receptor (FSH-R) expression in relation to tumour stage: early ovarian cancer (EOC) versus advanced ovarian cancer (POC) of different histological subtypes.

disease at primary diagnosis (Table 1). The median follow-up time was 7.3 years (range 0.3–16.8 years), with 26 documented relapses and 91 deaths. The median relapse-free survival was 2.1 years (range 0.9–7.2 years) and the median overall survival was 5.9 years (range 0.3–16.6 years; Table 1).

Ovarian cancer tissue analysis revealed LH-R-positive and FSH-R-positive tumours in 64.3% and 63.1% of samples, respectively (Figure 1). Only slight differences in LH-R or FSH-R expression could be observed with respect to histological subtype, grade or tumour stage (Table 2). Correlation analysis showed no significant correlation between LH-R or FSH-R and other histological parameters ($P > 0.05$), whereas a correlation between LH-R and FSH-R could be identified ($P = 0.006$, Spearman rho; Table 3). In general, statistical analysis for the immunoreactive score staining yielded no other correlations, but subgroup analysis indicated some significant differences in receptor expression (Figures 2 and 3).

Kaplan–Meier analysis revealed a poor prognosis in ovarian cancer patients whose tumour was solely FSH-R-positive. In contrast, good overall survival was observed for those who showed sole LH-R expression (log rank, $P = 0.03$; Figure 4). In accordance with the survival data, a trend for a shorter relapse-free interval was found for FSH-R-positive patients ($P = 0.734$). Cox regression analysis showed both receptors to be independent prognostic markers for patient survival [LH-R, $P = 0.026$, 95% confidence interval (CI) 0.349–0.937; FSH-R, $P = 0.015$, 95% CI 1.139–3.286] Table 4).

The results of this study show high levels of expression of LH-R (64.3%) and FSH-R (63.1%) in ovarian cancer tissue, with a certain amount of variability for different histological subtypes, grades or stages. In a study in 30 ovarian carcinomas, Zheng et al.[2] found a FSH-R positivity in 50% of all samples according to IHC staining. Similar results were gained with reverse transcription polymerase chain reaction (60%) and in situ hybridization (53%); the results obtained with all three methods correlated significantly. Our results gained with the IHC method in a large patient group are in good agreement with these data.

In-vitro analyses have shown various effects of LH and FSH on the proliferation, apoptosis and invasion of ovarian cancer and surface epithelium cells, including partially contradictory results.[2,3] Li et al.[4] observed concentration-dependent growth induction with FSH using the FSH-R3. Moreover, in-vitro models employing ovarian cancer cell lines showed opposing effects of FSH and LH on cell stimulation, namely a blockage of FSH stimulation by LH. Therefore, receptor up-regulation and down-regulation may also play a role in this antagonism, which would be in agreement with our IHC results. Besides the correlation of LH-R and FSH-R expression in ovarian cancer tissue, we additionally demonstrated that patient survival differs
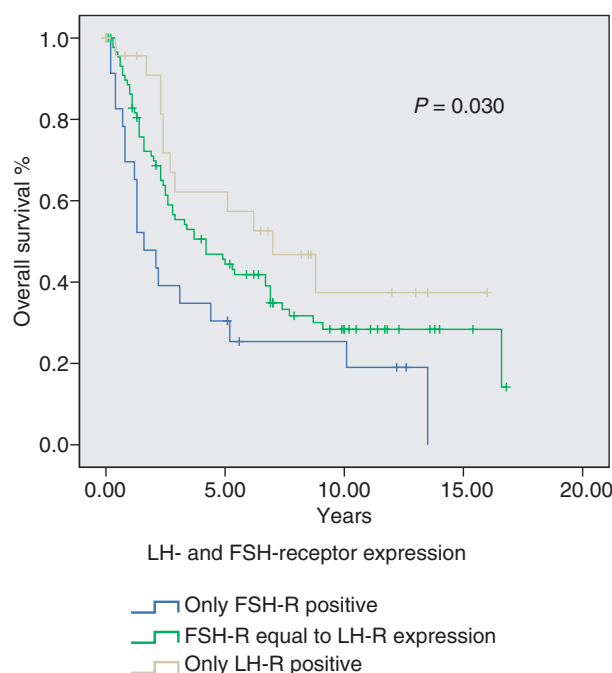

Figure 4. Kaplan–Meier analysis indicating survival in subgroups of patients with or without expression of luteinizing hormone receptor (LH-R) or follicle-stimulating hormone receptor (FSH-R).

Table 4. COX regression analysis for patient survival

Significance		Exp (B)	95.0% confidence interval for Exp (B)	
			Lower	Upper
FIGO	**<0.001**			
FIGO I versus II	0.989	1.009	0.301	3.385
FIGO I versus III	**<0.001**	3.968	1.918	8.209
FIGO I versus IV	0.981	0.000	0.000	
Grading	0.069			
Grading 1 versus 2	0.189	1.532	0.811	2.894
Grading 1 versus 3	**0.022**	2.075	1.109	3.882
LH-receptor	**0.026**	0.572	0.349	0.937
FSH-receptor	**0.015**	1.935	1.139	3.286

Significant results are shown in bold.

significantly between those with tumours that express solely LH-R and those with tumours that express solely FSH-R. Gebauer et al.[5] analysed the effect of

human chorionic gonadotropin (hCG)–doxorubicin on ovarian cancer cells, and observed increased activity of doxorubicin when it was conjugated to hCG through binding to the LH receptor. Thus, new therapeutic agents such as lytic peptides or chemotherapeutic agents that bind to FSH-R or LH-R may offer less toxic, but effective and selective, anticancer treatment options.

In conclusion, LH-R and FSH-R are frequently expressed in ovarian cancer tissue. Both receptors have prognostic significance and may assist in the choice of adjuvant treatment. As they are quite specific for ovarian tissue, they can serve as targets for new cancer therapies.

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