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Does IGF-1 play a role in the biology of ovarian cancer?

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ABSTRACT

Objectives: The aim of the study was to investigate serum concentrations of the insulin-like growth factor-1 in women with ovarian cancer and healthy controls, and to compare free IGF-1 levels with selected clinical and pathological parameters. Correlation analysis was used to measure the following: IGF-1 concentration and Ca125; IGF-1 level and the height of the OC patients.

Material and methods: The study included 70 patients with OC and 50 healthy controls. Serum concentrations of free IGF-1 were measured in all subjects. Routine diagnostic tests (CBC and USG and Ca125) were performed.

Results: Significantly higher serum concentrations of free IGF-1 were found in the study group as compared to controls. No statistically significant relationships between IGF-1 serum concentrations and tumor differentiation, histological type, and disease stage were detected. No statistically significant correlations between IGF-1 and Ca125 level or between IGF-1 and growth of OC patients were found.

Conclusions: Serum IGF-1 participates in the etiopathogenesis of ovarian cancer in menstruating women, while local synthesis of this factor and other components of the autocrine loop of the IGF-1 system play a greater role in their postmenopausal peers.

Key words: ovarian cancer, insulin-like growth factor–1, carcinogenesis

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INTRODUCTION

Insulin-like growth factor-1 (IGF-1), also known as somatomedin 1, is a mitogen which plays a pivotal role in the regulation of cell proliferation, differentiation, and apoptosis. IGF-1 is a member of a protein family which also includes insulin-like growth factor 2 (IGF-2), two types of membrane receptors (IGF-1R and IGF-2R), 6 binding proteins (IGFBP 1–6), hydrolyzing proteases, and other reactive molecule-binding proteins, which regulate the activity of the growth factors [1]. Disturbances in the functioning of the IGFBP/IGF/1GF1R system may lead to the induction of carcinogenesis, which has been demonstrated in various types of malignancies, i.e. breast, prostate, or colon cancer. Both, increased activity of the IGF-1/IGF-1R complex and lowered IGF-BP expression have been mentioned among the promoting factors for neoplastic processes [1]. IGF-1 is believed to exert its mitogenic effect on various cells by stimulating their proliferation and inhibiting their apoptosis via endocrine, paracrine and autocrine mechanisms [1]. Regardless, the findings of various studies which evaluated the role of IGF-1 in the biology of ovarian cancer (OC) remain ambiguous and often conflicting.

OBJECTIVES

The aim of the study was to investigate serum concentrations of free IGF-1 in women with OC vs. healthy controls, and to compare serum free IGF-1 levels with selected clinical and pathological parameters. Also, correlation analysis was used to measure the following: i) serum free IGF-1 concentrations and Ca125; ii) serum free IGF-1 levels and height of the OC patients.

MATERIAL AND METHODS

Patient characteristics and inclusion criteria

A total of 120 (70 with OC and 50 healthy controls) patients of the Clinic of Surgical, Endoscopic and Oncologic Gynecology, Polish Mother's Memorial Hospital in Lodz, constituted the study population. Local Ethics Committee approved of the study (no: 71/2012). Serum free IGF-1 levels were measured in all subjects, followed by routine diagno-

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stic tests: CBC and USG (both groups), and Ca125 (study group). Informed consent was obtained from all patients. All subjects from the study group were treated in accordance with the oncologic protocol. The exclusion criteria were as follows: history of chemotherapy or radiotherapy due to malignant neoplasms, history of any malignancy, recurrent OC (only patients with primary OC with no previous treatment were included), and hormonal therapy (contraceptives, HRT, etc.).

Immunoenzymatic analysis of serum free IGF-1 concentration

In the morning, 5 mL of fasting blood samples were drawn into serum gel tubes and transported to the laboratory within one hour of collection. Next, the samples were centrifuged at 1500 × g for 10 min., and serum was gently separated and stored at –80°C, until used. Free IGF-1 concentrations were tested with immunoenzymatic ELISA using commercially available kits (R&D): Human IGF-I Immunoassay (sensitivity 0,056ng/mL), according to the manufacturer's protocol. Absorbance was measured at 450nm in the ELx 808 reader. The results are expressed as ng/mL.

Statistical analyses

Statistical analyses were carried out using the following tests:

- the Shapiro-Wilk W to test the distribution for normality;
- T Student test to test quantitative parameters between 2 groups with normal distribution and homogeneity of variance (Levene, Brown and Forsythe tests);
- U Mann Whitney to test quantitative parameters between 2 groups with non-normal distribution or groups with statistically significantly different sample size (Chi^2 test was used to check equality of group proportions);
- ANOVA rang Kruskal-Wallis to test quantitative parameters between more than 2 groups with non-normal distribution or groups with statistically significantly different sample size (Chi^2 test was used to check equality of group proportions);
- Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation for non-normally distributed quantitative variables;
- Independent Pearson's chi2 to compare qualitative variables between 2 groups.

Statistical analysis was performed using STATISTICA 6.0, and the p-value of < 0.05 was considered as statistically significant.

RESULTS

Mean patient age in the study group was 50 years. Mean BMI was 26.83 kg/m^2. Forty-nine (70%) patients from the study group had normal menses and 21 (30%) were post-menopausal. As far as parity was concerned, the study group included 20 (28.57%) primiparas, 40 (57.14%) multiparas, and 10 (14.29%) nulliparas (Tab. 1).

No statistically significant differences in basic patient characteristics (age, BMI, parity, menopausal status and concomitant diseases) between the study group and controls were found (Tab. 1).

Out of 70 patients with OC, 37 (52.86%) were diagnosed with serous carcinoma, 5 (7.14%) with undifferentiated carcinoma, 8 (11.43%) with clear-cell carcinoma, 3 (4.29%) with seromucinous carcinoma, 7 (10%) with mucinous carcinoma, and 10 (14.29%) with endometrioid carcinoma (Tab. 2). The tumor was well-differentiated (G1) in 7 (10%), moderately-differentiated (G2) in 21 (30%), and poorly-differentiated (G3) in 42 (60%) women. As a result, 10 (14.29%) patients were diagnosed with stage I, 38 (54.29%) with stage III, and 22 (31.43%) with stage IV FIGO OC. No grade II FIGO cancer cases were found (Tab. 2).

Serum free IGF-1 levels were statistically significantly higher in the OC women as compared to the control group (Tab. 3). Significantly higher levels of IGF-1 were particularly pronounced in premenopausal OC women (Tab. 4). There was no statistically significant relationship between serum IGF-1 levels in OC women and tumor type, tumor differentiation, disease stage, and correlation of Ca125 or height in OC patients (Tab. 5–9).

DISCUSSION

Elevated serum IGF-1 levels in OC patients suggest its role in the process of oncogenesis. Both, *in vitro* and *in vivo* studies indicate that the local IGF-1 system is involved in the induction of tumor cell proliferation, invasion and neoangiogenesis [2–5]. Various sources have reported IGF-1 overexpression in both, tumor tissues of OC and tumor-derived fluid [6–9]. Researchers, inspired by the results of OC cell and tissue tests, started to investigate serum IGF-1 in women with OC. However, the number of these studies is limited, and the results remain inconsistent.

Lukanova et al., in a multi-center prospective study in 395 women, reported a higher risk of OC in subjects with elevated serum IGF-1 levels, who were < 55 years of age at the time of diagnosis. They did not observe such a relationship for the entire study group, regardless of their age, or for women aged ≥ 55 at the time of OC diagnosis. All women < 55 at the time of OC diagnosis were pre-menopausal at the time of blood collection [10]. These findings are consistent with the report of Peeters et al., who confirmed the hypothesis of Lukanova suggesting the involvement of serum IGF-1 in the carcinogenesis of ovarian cancer. They reported an increased risk for OC in women aged ≤ 55 at the time of diagnosis. The outcomes were particularly unambiguous for women who were pre-menopausal at the time of

Table 1. Statistical analysis of patient characteristics in the study and control groups

Parameter	Study group (n = 70)	Control group (n = 50)	Test	p
Age				
Mean	50 years	53.61 years	Cochran and Cox = –1.22547	> 0.05
Min. – max.	26–85 years	45–70 years		
Median	49 years	52 years		
SD	± 10.80 years	± 6.47 years		
BMI				
Mean	26.83 kg/m^2	27.51 kg/m^2	U M–W = –0.590871	> 0.05
Min. – max.	16.02–41.16 kg/m^2	20.55–40.04 kg/m^2		
Median	26.57 kg/m^2	26.25 kg/m^2		
SD	± 5.54 kg/m^2	± 4.56 kg/m^2		
Menopausal status				
Menstruating	49 (70%)	30 (60%)	Chi^2 Pearson = 1.296697	> 0.05
Post-menopausal	21 (30%)	20 (40%)		
Parity				
Nulliparas	10 (14.29%)	4 (8%)	Chi^2 Pearson = 1.978776	> 0.05
Primiparas	20 (28.57%)	16 (32%)		
Multiparas	40 (57.14%)	30 (60%)		
Comorbidities				
None	41 (58.57%)	27 (54%)	Chi^2 Pearson = 1.069641	> 0.05
Cardiovascular diseases	22 (31.43%)	18 (36%)		
Cardiovascular diseases & DM	6 (8.57%)	5 (10%)		
DM	1 (1.43%)	0 (0%)		

BMI — body mass index, DM — diabetes mellitus, SD — standard deviation, U M–W — U Mann Whitney test

Table 2. Clinical and pathological characteristics of the study group

Characteristics	Study group (n = 70)
Histological type	
Serous carcinoma	37 (52.86%)
Undifferentiated carcinoma	5 (7.14%)
Clear cell carcinoma	8 (11.43%)
Seromucinous carcinoma	3 (4.29%)
Mucinous carcinoma	7 (10%)
Endometrioid carcinoma	10 (14.29%)
Grading	
G1	7 (10%)
G2	21 (30%)
G3	42 (60%)
FIGO stage	
I	10 (14.29%)
II	0 (0.00%)
III	38 (54.29%)
IV	22 (31.43%)

Table 3. Statistical analysis of serum free IGF-1 levels in OC patients and controls

IGF-1 [ng/mL]	Control group	Study group
No. of patients	50	70
Min	4.40	5.00
Max	18.60	21.00
Median	9.90	13.40
Arithmetical mean	10.00	12.98
Standard deviation	4.38	4.61
Asymmetry coefficient	0.52	–0.29
Statistical analysis	**T Student Test = 2.362432; p < 0.05 (p = 0.022088)**	

Table 4. Statistical analysis of serum IGF-1 levels in OC women (premenopausal) and controls (premenopausal)

IGF-1 [ng/mL]	Control group (premenopausal)	Study group (premenopausal)
No. of patients	30	49
Min	4.40	9.60
Max	18.60	21.00
Median	11.20	15.20
Arithmetical mean	11.16	15.21
Standard deviation	4.80	3.01
Asymmetry coefficient	0.30	–0.60
Statistical analysis	**T Student Test = 2.986286; p < 0.05 (p = 0.005476)**	

blood collection. These authors did not find elevated risk for OC in women aged > 55 at the time of diagnosis [11].

Although Tas et al., did not find statistically significant differences in serum IGF-1 levels in women with OC as compared to non-cancer patients, they reported statistically significantly higher serum IGF-1 levels in women < 55 as compared to older patients. [12] Similarly, serum IGF-1 analysis in breast cancer (BC) patients showed increased levels in premenopausal women with BC as compared to their healthy premenopausal peers. In most publications, however, no such regularity was observed in postmenopausal

Table 5. Statistical analysis of serum free IGF-1 concentrations in patients with OC versus histological tumor type

IGF-1[ng/mL]	Histological tumor type	
	Serous carcinoma	Other
No. of patients	37	33
Min	5.00	5.70
Max	21.00	19.00
Median	12.85	13.80
Arithmetical mean	12.34	13.78
Standard deviation	5.14	3.92
Asymmetry coefficient	0.03–0.77	
Statistical analysis	T Student Test = 0.826354; p > 0.05	

Table 6. Statistical analysis of serum free IGF-1 levels in patients with OC versus tumor grade

IGF-1[ng/mL]	Tumor grade		
	G1	G2	G3
No. of patients	7	21	42
Min	5.70	5.00	5.40
Max	16.60	21.00	19.50
Median	15.30	14.05	13.40
Arithmetical mean	12.53	13.28	12.92
Standard deviation	5.95	5.58	4.24
Asymmetry coefficient	–1.64	–0.13	–0.39
Statistical analysis	Kruskal Wallis ANOVA = 0.044297; p > 0.05		

Table 7. Statistical analysis of serum free IGF-1 concentrations in patients with OC versus FIGO stage (2014)

IGF-1[ng/mL]	FIGO Stage			
	I	II	III	IV
No. of patients	10	0	38	22
Min	5.70	–	5.00	5.40
Max	16.60	–	21.00	19.00
Median	9.30	–	13.50	14.25
Arithmetical mean	10.53	–	13.56	13.01
Standard deviation	5.56	–	4.90	4.37
Asymmetry coefficient	0.95	–	–0.16	–0.71
Statistical analysis	Kruskal Wallis ANOVA = 0.622699; p > 0.05			

Table 8. Statistical analysis of the correlation (Pearson Correlation): between serum free IGF-1 concentration in OC patients and their height

IGF-1	Growth	
	R (X, Y)	p
	0.013369	p > 0.05

R (X, Y) — pearson's correlation coefficient

Table 9. Statistical analysis of the correlation between serum free IGF-1 concentration and Ca125 in patients with OC

Parameter	Ca 125	
	R	p
IGF-1	–0.019468	p > 0.05

R — spearman's rank

women, whose serum IGF-1 levels did not show statistically significant differences [13].

Our study team found that most OC patients who had a serum IGF-1 clearance were premenopausal (49 out of 70). Although no statistically significant differences in menopausal status and age were found, serum IGF-1 levels of premenopausal OC women as compared to premenopausal healthy peers were evaluated. As a result, significantly higher levels of serum IGF-1 were observed in patients with OC as compared to controls. The difference was even more apparent than in cases when the menopausal status was not taken into consideration, which may be consistent with the hypothesis that serum IGF-1 is involved in the biology of OC mainly in premenopausal women. There have been several attempts to explain this fact. Although IGF-1 can be produced by various tissues, the liver, whose cells synthesize this factor in response to the growth hormone (GH), remains the primary source of serum IGF-1. It has been demonstrated that IGF-1 production is reduced with age by the liver, possibly due to a weaker response to pituitary GH expression [14]. With aging, serum IGF-1 is less affected by the GH/IGF-1 axis than in adolescence [15]. Some researchers have reported an increased risk for the development of OC in taller women, which could indirectly account for the theory in question [16]. Namely, the achieved height is strongly correlated with the level of serum IGF-1 in puberty, i.e. in young women, but later there is no correlation [17]. It would therefore be possible for taller women to be exposed to higher levels of serum IGF-1 during puberty and at a young age, which could result in an elevated risk for cancer transformation to OC. However, researchers the possible correlation between the increase in height and the risk for developing OC has been subject to much heated debate [18]. In our study, the height of OC and non-cancer patients did not differ significantly and thus, this parameter was not associated with OC and did not affect the obtained results. Similarly, the analysis of free serum IGF-1 levels in OC patients and their height also did not reveal a significant correlation between these parameters. Another explanation for the modification of serum IGF-1 level based on age and menopausal status may be the hypothesis suggesting the presence of high levels of estrogen in women of reproductive age. Endogenous estrogen-dependent,

elevated serum IGF-1 levels have been demonstrated in the perovulatory period in women with normal menstrual cycles. Furthermore, after the menopause, a decrease not only in total serum IGF-1 but also in the concentration of its biologically active form, i.e. free IGF-1, have been observed [10, 11, 19–21]. On the other hand, some sources reported no changes in serum IGF-1 levels depending on different phases of the menstrual cycle, and found no correlation between IGF-1 levels and endogenous serum estrogen concentrations [22–24]. This hypothesis is therefore not an ideal explanation for the association between elevated serum IGF-1 levels and an increased risk for OC in young women.

Lower serum IGF-1 levels in OC patients as compared to women with benign tumors and/or non-tumor women have also been reported by some authors [25–29]. Other researchers did not observe any statistically significant differences in serum IGF-1 levels in OC women as compared to non-cancer patients, and did not report any higher serum IGF-1-dependent risk for the development of OC [12, 30]. However, these studies were conducted either in postmenopausal women or their menopausal status was as shown in the abovementioned analysis, and our findings have implications for the change in IGF-1 levels [10–12]. Moreover, these authors did not account for the possibility of cardiovascular diseases (common in older, postmenopausal patients) in the investigated populations, what might be a serious study limitation due to a proven link between lowered serum IGF-1 level and these pathologies [31, 32]. It cannot be ruled out that OC women were more likely to suffer from cardiovascular diseases. As a result, the reported lower serum IGF-1 levels in OC patients did not result *de facto* from this pathology but a comorbid cardiovascular disease [25, 26, 29]. Moreover, Flyvbjerg et al., did not include data on BMI, diabetes mellitus (DM), and hormone replacement therapy (HRT) in their publication [25], which questions the reliability of the results, given the fact that both, BMI and DM have a proven effect on serum IGF-1 level [33, 34]. Numerous studies have also indicated that oral HRT leads to a significant decrease in serum IGF-1 levels, which is probably due to direct inhibition of the synthesis of this factor in the liver by oral estrogen [35]. We observed no significant differences in either, BMI values or distribution of comorbidities in OC patients with IGF-1 and controls. These parameters did not affect the results. In addition, none of the patients included in the study received HRT or hormonal contraception because it constituted an exclusion criterion.

Three other publications also reported a decrease in total serum IGF-1 levels in OC patients [27, 28, 36]. However, these studies did not account for the menopausal status, age, and the possibility of cardiovascular diseases in the investigated populations. Therefore, it remains unknown whether this factor affected their findings. In addition, Dal Maso et al., observed a reduced level of total serum IGF-1 in OC women as compared to controls, while serum free IGF-1 levels were similar in both groups [27]. It follows that the percentage of serum free IGF-1 was significantly higher as compared to total serum IGF-1 in OC women versus controls. However, due to the inaccurate analysis by the authors, it is difficult to draw clear conclusions from their work [27]. Baron-Hay et al., and Shah et al., also did not include data on BMI, DM, HRT or hormonal contraception, thus rendering their analyses unreliable [28, 36]. In addition, as was claimed by Tworoger et al., considering the biology of OC and the proven direct involvement of IGF-1 in the development of this tumor in experimental studies on OC, an inverse correlation between serum IGF-1 and the process of carcinogenesis of OC seems unlikely [30]. Also, these authors found no relationship between serum IGF-1 levels and the risk for OC, even in cases of OC diagnosis in women < 55 years of age. However, despite a large sample size, the group of women < 55 years of age and diagnosed with OC consisted of only 59 patients, which was a limitation for the analysis. In addition, they did not specify the menopausal status of these 59 women at the time of blood collection, which might have had a significant impact on the obtained results [30]. One might speculate that most of the 59 subjects were in fact postmenopausal at the time of blood collection, which would have significantly affected the final results.

No significant correlations between the level of serum free IGF-1 in OC women and clinical and pathological parameters were found, which is consistent with all publications included in the study [10–12, 25–30].

CONCLUSIONS

IGF-1 is most likely involved in the etiology of OC. Unfortunately, the level of serum IGF-1 is influenced by numerous factors both, genetic and exogenous, such as diet, exercise, medication, BMI, chronic diseases (DM, cardiovascular and other), and age [14, 15, 29, 31–35, 37]. In addition, not all factors which influence the regulation of serum IGF-1 have been fully elucidated. However, based on our results and the available literature, it seems safe to conclude that the level of IGF-1 in OC tissues is probably affected by endocrine and autocrine regulation, which is consistent with the results obtained by Brokow and Conover [6, 38]. Studies conducted to clarify the role of IGF-1 (both, locally synthesized and peripherally circulating serum) in the biology of breast cancer, have confirmed the role of this factor in the oncogenesis of this tumor [35]. The carcinogenesis of OC may be analogous and the IGF-1 present in the serum is involved in the carcinogenesis of this tumor mainly in young, menstruating women. In older, postmenopausal women, local synthesis of IGF-1 and the other components of the autocrine loop of the IGF-1 system is likely to play a greater role.

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