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European Journal of Cancer 37 (2001) 478–485

European Journal of Cancer

www.ejconline.com

IGFBP-3 in epithelial ovarian carcinoma and its association with clinico-pathological features and patient survival

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Received 11 July 2000; received in revised form 9 October 2000; accepted 2 November 2000

Abstract

Insulin-like growth factor binding protein-3 (IGFBP-3) regulates the mitogenic and anti-apoptotic actions of insulin-like growth factors (IGFs). To study the role of IGFBP-3 in ovarian cancer progression, we measured IGFBP-3 concentrations in tumour tissues from 147 patients with epithelial ovarian carcinoma and examined its associations with clinicopathological features of disease and patient survival. The average age of the patients was 54.6 years (range 25–88 years) and the median follow-up time was 37 months. IGFBP-3 levels were measured with a commercial immunoassay kit. Low IGFBP-3 levels were significantly associated with unfavourable prognostic features of the disease, including advanced stage ($P = 0.048$), large size of residual tumour ($P = 0.007$), and suboptimal debulking outcome ($P = 0.007$). Low IGFBP-3 levels were also associated with a significantly increased risk for disease progression (RR = 1.92; 95% confidence interval (CI) 1.05–3.45; $P = 0.034$), but the association was not sustained when other clinical and pathological variables were adjusted for in the analysis. No significant associations were observed between the IGFBP-3 level and patients' overall survival and response to chemotherapy. Findings of the study indicate that IGFBP-3 may play a role in the progression of epithelial ovarian cancer, but that it has no independent value in predicting either disease prognosis or the response of patients to chemotherapy.

Keywords: IGFBP-3; Ovarian cancer; Prognosis; Survival

1. Introduction

Ovarian cancer is one of the most lethal malignancies in women [1]. Two thirds of patients present with advanced stage disease for which few effective treatments are available, and more than 50% of the patients die from the disease within 5 years of their diagnoses. Over 90% of ovarian cancer cases are epithelial ovarian carcinomas [2], the aetiology and progression of which remain poorly understood. However, there is a growing understanding of the molecular events associated with the development and progression of ovarian cancer, including the actions of growth factors, growth factor receptors, oncogenes and tumour suppressor genes, as well as loss of heterozygosity or allelic imbalance at various chromosomal loci. It is reasonable to speculate that a fundamental understanding of the process of ovarian carcinogenesis achieved through the application of molecular biology techniques will allow us to predict the biological behaviour of ovarian cancer better than our current approaches [3].

Insulin-like growth factor binding protein-3 (IGFBP-3) is a 46–53 kDa glycoprotein with specific binding

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0959-8049/01/$ - see front matter
PII: S0959-8049(00)00423-8

affinity for IGFs [4]. These are peptide hormones with strong mitogenic effects on a variety of cancer cells, including epithelial ovarian carcinoma cells [5]. In addition to their mitogenic action, IGFs are also able to suppress programmed cell death, thereby enhancing cancer cell growth [6]. The actions of IGFs are mediated through a specific cell membrane receptor, IGF-IR (IGF-1 receptor), which is overexpressed in many cancer cells and is involved in the cellular transformation induced by proteins of tumour viruses or oncogene products [7]. IGFBP-3 is one of six IGF binding proteins. Due to the higher binding affinity of IGFs to IGFBP-3 than to IGF-IR, binding of IGFBP-3 to IGFs blocks the interaction between IGFs and IGF-IR. As a result, IGFBP-3 suppresses the mitogenic and antiapoptotic actions of IGFs [4]. In addition, studies have shown that IGFBP-3 is able to mediate the effect of many antiproliferative molecules including wild-type p53 protein, transforming growth factor-β, retinoic acid and vitamin D [8–11].

IGF-I, IGF-IR and IGFBP-3 are detected in the ovary [12]. Compared with normal ovarian epithelial cells, IGF-I levels are higher and IGF-IR is overexpressed in ovarian carcinoma cells [13–15]. Results from cell culture studies suggest that IGF-I is able to stimulate the growth of ovarian cancer and this stimulation can be abolished by eliminating the IGF-I receptor or blocking its function [5,12,16]. Serum levels of IGFBP-3 are lower in women with ovarian cancer than in those without the disease [15,17]. To assess the role of IGFBP-3 in the progression of ovarian cancer, we measured IGFBP-3 concentrations in ovarian carcinoma tissues using an enzyme-linked immunosorbent assay (ELISA) and examined the relationships between the expression level of this protein and clinical and pathological features of ovarian cancer, as well as the associations between the IGFBP-3 level and patient survival.

2. Patients and methods

2.1. Ovarian cancer tissues and patients

Primary tumour tissue specimens from 147 patients with epithelial ovarian carcinoma were collected consecutively from the Gynecologic Oncology Service at the University of Turin from April 1988 to January 1997. These specimens had been snap-frozen in liquid nitrogen immediately after surgical resection. Tissue sections containing more than 70% of tumour cells determined microscopically were stored at −80°C for the study.

The average age of the patients in the study was 54.6 years (standard deviation (S.D.) = 12.5); the range was between 25 and 88 years. All patients underwent surgical staging. Among the 75 patients (51%) who had detectable residual tumour left behind after surgery, the residual tumour size ranged from 1 to 9 cm and the median size was 1 cm. Based on the International Federation of Gynecology and Obstetric (FIGO) staging system [18], 36 (24%) were diagnosed with stage I disease, 13 (9%) with stage II, 89 (61%) with stage III and 9 (6%) with stage IV ovarian carcinoma. Histopathological examination revealed that the majority of patients had high histological grade lesions; 33 (22%) were grade 2 and 79 (54%) were grade 3. Only 16 (11%) and 19 (13%) of the patients had grade 0 and 1 carcinomas, respectively. With regard to the histological type, 57 patients (39%) were serous papillary, 27 (18%) were endometrioid, 18 (12%) were clear cell, 15 (10%) were mucinous, 6 (4%) were mullerian and 24 (16%) were undifferentiated.

The follow-up time for these patients ranged from 3 to 87 months and the median was 37 months. During the course of follow-up, 82 patients (56%) developed progressive disease and 57 (39%) died. The median time interval was 12 months from surgery to first recurrence or progression and was 18 months from surgery to death. The range of time interval from surgery to first recurrence or progression is between 1 and 67 months and the range of time interval from surgery to death is between 3 and 79 months. All patients had been previously untreated for ovarian cancer. The majority of patients ($n = 115$; 78%) received postoperative chemotherapy, and only 4 (3%) and 3 (2%) patients had postoperative radiation and hormonal therapy, respectively. The first-line chemotherapy regimens, after which treatment response was assessed as described below, included cisplatin (given to 75 patients; 51%), carboplatin ($n = 42$; 29%), cyclophosphamide ($n = 62$; 42%), doxorubicin ($n = 11$; 7%), epirubicin ($n = 18$; 12%), paclitaxel ($n = 24$; 16%), melphalan ($n = 1$; 1%), and methotrexate ($n = 1$; 1%). Treatment response was assessed in patients with measurable ($\geqslant 1$ cm) residual lesions by computed tomography (CT) scanning, serum CA125 monitoring and, in some cases, by second look laparotomy, and was based on the following criteria: resolution of all evidence of disease for at least 1 month was considered a complete response; a decrease of greater than or equal to 50% in the product of the diameters (maximal and minimal) of all measurable lesions lasting at least 1 month without the development of new lesions was considered as a partial response; a decrease of less than 50% or an increase of less than 25% in the product of the diameters of all measurable lesions was considered as stable disease; and an increase of greater than or equal to 25% in the measurable lesions as described above or the identification of new lesions was considered as progressive disease. Second-line chemotherapy was given to 48 patients (33%) and included cisplatin ($n = 6$; 13%), carboplatin ($n = 13$; 27%), cyclo-

phosphamide ($n=9$; 19%), paclitaxel ($n=24$; 50%), epirubicin ($n=11$; 23%) and doxorubicin ($n=4$; 8%). 11 patients (7%) required third-line chemotherapy, which consisted of cisplatin ($n=1$; 9%), carboplatin ($n=13$), cyclophosphamide ($n=9$; 82%), paclitaxel ($n=7$; 64%) and epirubicin ($n=1$; 9%) Many patients received more than one chemotherapy regimen.

2.2. Measurement of IGFBP-3 and other biomarkers

Frozen tissue specimens (200–300 mg) were pulverised manually to a fine powder in liquid nitrogen. The tissue powder was mixed with 1 ml cell lysis buffer for 30 min on ice and then was centrifuged at 14 000*g* for 30 min at 4°C. The cell lysis buffer contained 50 mM Tris, 150 mM NaCl, 5 mM ethylenediaminetetraacetic acid (EDTA), 10 ml/l Nonidet P (NP)-40 surfactant, 10 mg/l phenylmethylsulphonyl fluoride, and 1 mg/l each of aprotinin and leupeptin. After centrifugation, the supernatant was collected for measurement of IGFBP-3, total protein and other biomarkers.

Concentrations of IGFBP-3 in tissue extracts were measured using a commercial ELISA kit (Diagnostic Systems Laboratories Inc., Webster, TX). Protein concentrations in the samples were determined by the bicinchoninic acid method (Pierce Chemical, Rockford, IL). Levels of IGFBP-3 in tissue extracts were adjusted for the total protein content in each sample and the final unit was ng of IGFBP-3 per mg of total protein. Tissue extract concentrations of p53 protein measured with an ELISA method in a previous study [19] were also available for evaluation of the correlation between p53 and IGFBP-3.

2.3. Statistical analysis

IGFBP-3 levels were compared among patients with different clinical and pathological features using the Wilcoxon Rank-Sum test. Correlations of IGFBP-3 with other numerical and ordinal variables were examined using the Spearman correlation coefficient. Associations between patient survival and IGFBP-3 levels were determined by calculating the relative risks for disease progression and death and their confidence intervals using the Cox proportional hazards regression analysis. The progression-free survival was defined as the time interval from surgery to the first progression of the disease. The overall survival was the time interval between surgery and death. IGFBP-3 was first analysed as a continuous variable in the Cox regression model. After we observed no significant association between IGFBP-3 and the disease outcome, a three-level ordinal variable of IGFBP-3 classified based on its tertile distribution was used in the survival analysis. All P values were derived from two-sided statistical tests. A P value of <0.05 was considered significant.

3. Results

3.1. IGFBP-3 in ovarian cancer

The concentrations of IGFBP-3 in the 147 ovarian cancer specimens ranged from 2.4 to 273.4 ng/mg. The mean IGFBP-3 level was 24.9 ng/mg (S.D. = 33.1), higher than the median value, 18.5 ng/mg, indicating that the distribution of IGFBP-3 concentration was positively skewed.

3.2. IGFBP-3 and clinicopathological features

Table 1 shows the non-parametric correlation of IGFBP-3 with age, clinical stage, histological grade, size of residual tumour and tumour extract level of p53 protein. IGFBP-3 concentration was not correlated with patient age ($P=0.957$), histological grade ($P=0.347$), or p53 protein concentration ($P=0.865$). However, inverse correlations of IGFBP-3 with stage ($P=0.058$) and residual tumour size ($P=0.019$) were suggested, although these relationships were relatively weak ($r=-0.157$ and -0.194, respectively) and for stage were borderline-significant.

Associations of IGFBP-3 with disease stage and residual tumour size could also be found when the medians of IGFBP-3 were compared between groups of patients with early and late stage ovarian cancers or with small and large residual tumours (Table 2). Patients with early stage disease tended to have IGFBP-3 levels higher than those with late stage disease (22.3 versus 17.2, $P=0.048$). Small residual tumours had IGFBP-3 levels higher than large residual lesions (22.1 versus 16.5, $P=0.007$). In addition to stage and residual tumour size, IGFBP-3 was also associated with debulking outcome (Table 2). Compared with suboptimal outcome, optimal debulking outcome was associated with higher levels of IGFBP-3 (22.3 versus 16.4, $P=0.007$).

IGFBP-3 levels varied substantially among different histological types of ovarian cancer (Table 2). Clear cell and endometroid types had relatively high IGFBP-3 levels, whereas mucinous and mullerian types had lower IGFBP-3 levels. However, the differences did not reach statistical significance ($P=0.086$). With respect to

Table 1
Correlations between IGFBP-3 and clinicopathological features

Features	Number of patients	Correlation coefficient[a]	P value
Age (year)	147	−0.004	0.957
Stage	147	−0.157	0.058
Histological grade	147	−0.078	0.347
Residual tumour (cm)	147	−0.194	0.019
p53 protein (ng/mg)	145	0.014	0.865

[a] Spearman correlation coefficient.

histological grade, an inverse relationship appeared to exist between tumour grade and IGFBP-3 concentration, but the differences were not statistically significant ($P=0.289$). There were also no differences in IGFBP-3 levels between patients who received and did not receive postoperative chemotherapy ($P=0.860$) and between those who had and did not have a complete response to the postoperative treatment ($P=0.300$). Although patients who developed progressive disease tended to have lower IGFBP-3 levels than those who did not ($P=0.050$), levels of IGFBP-3 did not show significant differences between patients who had died and who were still alive at the end of follow-up ($P=0.500$).

3.3. IGFBP-3 and ovarian cancer survival

The relative risks for disease progression and death among patients with low, medium and high IGFBP-3 (classified by its tertile distribution), as well as with other clinical and pathological features of the disease, are shown in Table 3. Patients with the lowest tertile of IGFBP-3 had a significantly higher risk for disease progression compared with those with the highest tertile (relative risk (RR) = 1.92, $P=0.034$). A statistically significant trend between declining IGFBP-3 level and increasing risk for disease progression was also suggested ($P=0.033$ for the trend). However, a similar association between IGFBP-3 and risk for death was not observed ($P=0.119$ for the trend), although the same directional relationship was indicated. The

Table 2
Associations between IGFBP-3 and clinicopathological features

Features	Number of patients *n* (%)	IGFBP-3 (ng/mg) Median (range)	*P* value[a]
Stage			
I–II	49 (33)	22.3 (2.7–273.4)	
III–IV	98 (67)	17.2 (2.4–151.8)	0.048
Histological grade			
0	16 (11)	23.5 (3.4–38.3)	
1–2	52 (35)	18.1 (3.0–273.4)	
3	79 (54)	17.6 (2.4–76.2)	0.289
Residual tumour			
< 1 cm	72 (49)	22.1 (2.7–273.4)	
⩾1 cm	75 (51)	16.5 (2.4–76.2)	0.007
Histological type			
Clear cell	18 (12)	24.7 (2.7–242.6)	
Endometroid	27 (18)	21.5 (4.9–273.4)	
Mucinous	15 (10)	9.3 (3.0–26.4)	
Mullerian	6 (4)	13.8 (8.7–27.6)	
Serous papillary	57 (39)	17.6 (4.3–106.9)	
Undifferentiated	24 (16)	18.6 (2.4–39.9)	0.086
Debulking outcome			
Suboptimal	72 (49)	16.4 (2.4–76.2)	
Optimal	75 (51)	22.3 (2.7–273.4)	0.007
Chemotherapy			
No	32 (22)	18.3 (3.1–44.5)	
Yes	115 (78)	18.5 (2.4–273.4)	0.860
Treatment response			
Complete response	112 (76)	19.3 (2.4–273.4)	
All other responses	35 (24)	16.8 (3.1–76.2)	0.300
Progression			
No	65 (44)	21.6 (3.0–273.4)	
Yes	82 (56)	16.7 (2.4–242.6)	0.050
Death			
No	90 (61)	20.3 (2.7–273.4)	
Yes	57 (39)	17.2 (2.4–242.6)	0.500

[a] Wilcoxon Rank-Sum test or Kruskal–Wallis test as appropriate.

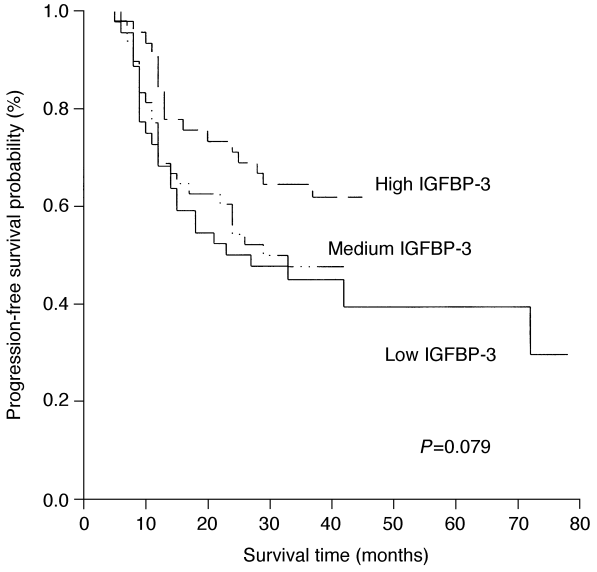

Fig. 1. The Kaplan–Meier survival curves for disease progression-free survival among patients with high (third tertile), medium (second tertile) and low (first tertile) IGFBP-3 levels.

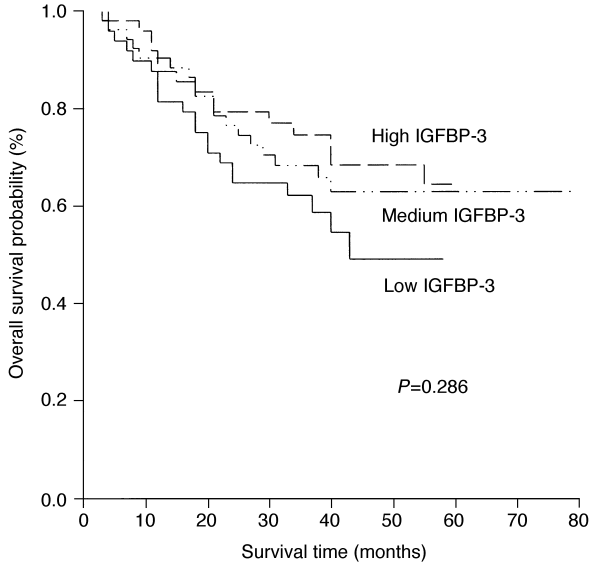

Fig. 2. The Kaplan–Meier survival curves for overall survival among patients with high (third tertile), medium (second tertile) and low (first tertile) IGFBP-3 levels.

Table 3
Univariate survival analysis with the Cox regression model

Variable	Progression		Death	
	RR (95% CI)	*P* value	RR[a] (95% CI)	*P* value
IGFBP-3 (tertile)				
High	1.00		1.00	
Medium	1.16 (0.68–1.96)	0.589	1.37 (0.74–2.56)	0.309
Low	1.92 (1.05–3.45)	0.034	1.67 (0.87–3.23)	0.121
Test for trend	$P=0.033$		$P=0.119$	
Stage				
I–II	1.00		1.00	
III–IV	7.22 (3.52–14.8)	<0.001	14.7 (4.55–47.4)	<0.001
Histological grade				
0	1.00		1.00	
1 or higher	3.57 (2.22–5.72)	<0.001	4.68 (2.52–8.70)	<0.001
Residual tumour				
<1 cm	1.00		1.00	
$\geqslant 1$ cm	7.77 (4.42–13.7)	<0.001	11.8 (5.29–26.3)	<0.001
Debulking outcome				
Optimal	1.00		1.00	
Suboptimal	8.33 (4.55–14.3)	<0.001	11.1 (5.26–25.0)	<0.001
Response to treatment				
Complete response	1.00		1.00	
All other responses	6.25 (3.70–10.0)	<0.001	11.1 (6.25–20.0)	<0.001
p53 Protein (tertile)				
Low	1.00		1.00	
Medium	1.38 (0.73–2.60)	0.320	1.43 (0.69–2.94)	0.336
High	2.94 (1.63–5.32)	<0.001	2.75 (1.42–5.35)	0.003
Test for trend	$P<0.001$		$P=0.002$	

[a] RR, relative risk; CI, confidence interval.

Kaplan–Meier survival curves are shown in Figs. 1 and 2 for progression-free survival and overall survival, respectively.

In addition to IGFBP-3, we also found in the univariate survival analysis using the Cox regression model that histological grade, residual tumour size, debulking outcome, response to postoperative treatment, and p53 protein level were all associated with risks for both disease progression and death (Table 3). Table 4 shows the results of the Cox regression analysis on the association of IGFBP-3 with progression-free survival and overall survival after adjusting for the clinical and pathological features of the disease including patient age, stage, histological grade, histological type, residual tumour size, debulking outcome and p53 protein levels. In the multivariate analysis, it appeared that low IGFBP-3 indicated a higher risk for disease progression (RR = 1.72, $P=0.123$) but, however, the difference was no longer statistically significant, including no significance in the test for trend ($P=0.121$). Similar to the

Table 4
Multivariate survival analysis with the Cox regression model

	Progression		Death	
	RR[a] (95% CI)	*P* value	RR (95% CI)	*P* value
IGFBP-3 (tertile)[a]				
High	1.00		1.00	
Medium	1.27 (0.69–2.33)	0.444	1.54 (0.81–2.94)	0.191
Low	1.72 (0.86–3.45)	0.123	1.79 (0.87–3.70)	0.115
Test for trend	$P=0.121$		$P=0.102$	

[a] RR, relative risk; CI, confidence interval. Adjusted for age, stage, grade, residual tumour, debulking outcome, histological type and p53 level.

Table 5
Associations of IGFBP-3 with chemotherapy response

Chemotherapy	Complete response (%)	No response (%)	*P* value[a] *n*
All treated patients			
IGFBP-3 < median	25 (61)	16 (39)	
IGFBP-3 ⩾ median	15 (52)	14 (48)	0.472
Chemotherapy subgroup A[b]			
IGFBP-3 < median	8 (42)	11 (58)	
IGFBP-3 ⩾ median	10 (53)	9 (47)	0.746
Chemotherapy subgroup B[c]			
IGFBP-3 < median	7 (70)	3 (30)	
IGFBP-3 ⩾ median	4 (57)	3 (43)	0.644
Chemotherapy subgroup C[d]			
IGFBP-3 < median	10 (83)	2 (17)	
IGFBP-3 ⩾ median	1 (33)	2 (67)	0.154

[a] Fisher's Exact Test.
[b] Patients received cisplatin or carboplatin, with or without cyclophosphamide.
[c] Patients received group A drugs plus doxorubicin or epirubicin.
[d] Patients received paclitaxel alone or in combination with group B drugs.

univariate analysis, no significant association was found between IGFBP-3 and the risk for death after adjusting for the other variables.

3.4. IGFBP-3 and response to chemotherapy

To determine if the IGFBP-3 level had any predictive value for chemotherapy, we compared the rates of a complete response to chemotherapy between patients who had high and low IGFBP-3 levels defined by a median cut-off point. The results of the analysis are shown in Table 5. No significant association was found in any of the comparisons. Thus, IGFBP-3 did not have any apparent value for predicting the response of patients to postoperative chemotherapy in epithelial ovarian cancer.

4. Discussion

Our study demonstrated that IGFBP-3 concentrations in extracts prepared from ovarian carcinoma tissues were inversely correlated with disease stage and residual tumour size. Tumour tissues containing low levels of IGFBP-3 tended to occur in patients who had either advanced disease or large residual lesions left behind after surgery. Results of surgical debulking were also associated with IGFBP-3, in that patients with optimal debulking results had significantly higher IGFBP-3 than patients with suboptimal debulking results. These findings suggested that high IGFBP-3 could be associated with a favourable prognosis. Indeed, the survival analysis performed here supported this notion. A higher risk for disease progression was found in patients with low IGFBP-3, and a dose-dependent relationship was also statistically significant. However, no significant association was found between IGFBP-3 and death, although a similar relationship was indicated. Furthermore, the association between IGFBP-3 and disease progression disappeared when other clinical and pathological variables were adjusted for in the analysis. Survival analysis showed that disease stage, histological grade, debulking result, and size of residual tumour were strongly associated with disease progression and overall survival. These strong associations may override the effect of IGFBP-3 in the multivariate regression analysis.

Earlier studies had shown that serum levels of IGFBP-3 were lower in ovarian cancer patients than in normal women [15,17]. Although IGFBP-3 was found to be able to suppress the mitogenic effect of IGF-I on cell growth [20], the role of IGFBP-3 in ovarian cancer remains largely unknown. The results of our study suggest that high IGFBP-3 may suppress ovarian cancer progression. This finding is consistent with the role of IGFBP-3 in suppressing cell growth and is compatible with the results of most ovarian cancer studies addressing the impact of the IGF family. In those studies, IGF-I was found to be able to stimulate the proliferation of ovarian cancer cells [5,12]. IGF-I levels were revealed to be higher in ovarian cancer tissues than in normal ovarian tissues or benign lesions of the ovary [15]. In addition, the IGF-I receptor which mediated the mitogenic action of IGF-I was shown to be overexpressed in ovarian cancer tissues [13,14], and suppressing the expression of IGF-IR was demonstrated to slow the growth of ovarian cancer cells [16].

However, the role of IGFBP-3 in regulating cell growth is complex. In addition to an IGF-dependent effect, IGFBP-3 also exerts an IGF-independent

inhibitory effect on cell growth [21]. Although most *in vitro* studies showed that IGFBP-3 was able to suppress the mitogenic action of IGFs, some experiments found that this binding protein could also enhance cell growth [22,23]. Under certain circumstances, the binding of IGFBP-3 to IGFs protects the peptide hormones from degradation and as a result, IGFBP-3 increases the bioavailability of IGFs in local tissues. Thus, it is believed that the IGF binding proteins have a dual regulatory impact on IGF actions and this impact is further modulated by a large group of IGFBP proteases. Three categories of IGFBP proteases have been described, including kallikreins, cathepsins and matrix metalloproteinases [24]. These proteases proteolyse IGFBPs, thereby releasing IGFs from the binding proteins and consequently allowing IGFs to resume their activity to interact with the IGF-I receptor [24].

It may be due to the dual regulation of IGFBP-3 on IGFs that opposite impacts of IGFBP-3 on cancer progression have been observed at different cancer sites. In this study, high levels of IGFBP-3 were associated with favourable prognostic features of epithelial ovarian cancer, such as small residual tumour and early stage. However, in breast cancer, high IGFBP-3 has been linked to poor prognosis. Rocha and colleagues [25,26] reported that IGFBP-3 was high in tumours featured with negative steroid hormone receptors, high S-phase fraction and aneuploidy, and that IGFBP-3 levels were correlated positively with tumour size and inversely with positive oestrogen and progesterone receptor status. Our own studies [27,28] confirmed these findings and suggested a possible association with patient overall survival; an increased risk for death associated with high levels of IGFBP-3 in breast cancer was found, in agreement with the findings of other studies [25,26].

The regulation of cell growth and differentiation by the IGF family is both endocrine and paracrine. Because of possible contamination of tissue specimens by blood, the validity of measuring IGFs and IGFBPs in tissue extracts using homogenised tissue specimens has been questioned [29]. However, no study has yet reported the relative amount of IGFBP-3 in tissue extracts originating from the blood circulation. Furthermore, it was shown in one tissue study that the level of IGFBP-3 in breast cancer tissues measured by an ELISA was highly correlated with the amount of *IGFBP-3* mRNA in the same tissues determined by a RNase protection assay [25]. Moreover, that study did not find any correlation between haemoglobin and IGFBP-3 in breast tissues. These findings support the notion that most IGFBP-3 measured in tissues represents the local tissue level and that blood contamination has little impact on the tissue level of IGFBP-3.

The frequency distribution of IGFBP-3 in ovarian tumour tissue was positively skewed and this distribution was similar to that in serum. The concentration of IGFBP-3 was much lower (100-fold) in ovarian tissue than in blood circulation [30]. Serum IGFBP-3 was inversely correlated with age in adults. A similar correlation was not seen in tissues. IGFBP-3 levels varied with histological type, being high in clear cell tumours and low in mucinous tumours, but because of the small sample sizes of the subgroups, the difference was not statistically significant. Further assessing the relationship between IGFBP-3 and histological type may reveal insights into the role of IGFBP-3 in ovarian cancer.

CA125 is a useful tumour marker for ovarian cancer. We examined the correlation between IGFBP-3 levels in the tissues and the serum levels of CA125 before and after surgery. No correlation was found between the two proteins (data not shown). A cell culture study found that *IGFBP-3* gene expression was upregulated by wild-type p53 [8]. The relationship between IGFBP-3 and p53 was assessed in this study, but no correlation between the two proteins was found.

In summary, the study showed that IGFBP-3 levels in ovarian cancer tissue were inversely associated with disease stage and residual tumour size. Patients with optimal debulking results also had higher levels of IGFBP-3 than patients with suboptimal debulking results. In addition to the associations with favourable prognostic indicators, IGFBP-3 levels were associated with progression-free survival. Findings of the study suggest that IGFBP-3 may play a role in ovarian cancer progression, but this role is relatively weak and has limited value in predicting the prognosis of ovarian cancer patients, as well as their response to chemotherapy.

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