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SURVIVIN EXPRESSION IN OVARIAN CANCER

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Aim: **To examine the expression of survivin in benign ovarian tumors, ovarian carcinomas of different stages.** ***Methods:*** **We screened the expression of survivin mRNA by reverse transcription polymerase chain reaction in 114 ovarian tissue samples. Quantitative real-time PCR was used to estimate survivin mRNA levels in the samples with positive survivin expression.** ***Results:*** **No survivin mRNA was expressed in all normal ovarian specimens, while it appeared in 73% of ovarian carcinomas, 47% of borderline ovarian carcinomas and 19% of benign ovarian tumors. The survivin mRNA expression rate was positively associated with clinical stage ($P = 0.026$) and differentiation grade ($P = 0.049$). There was notably statistically significant difference in the survivin mRNA expression rate dependent on different histological types (serous, mucinous, endometrioid, $P = 0.008$), but not – dependent on lymph node metastasis ($P = 0.921$) and ascites ($P = 0.87$). In tissues with positive expression of survivin, we also found that mean survivin mRNA expression levels were higher in ovarian carcinomas than that in benign ovarian tumors and borderline ovarian carcinoma tissues ($P < 0.001$). Among ovarian carcinomas, the high survivin mRNA expression levels correlated with the clinical stages, differentiation grade, lymph node metastasis, but not — with ascites and histological type.** ***Conclusion:*** **Our study suggest that survivin is associated with progression of ovarian carcinoma.**

Key Words: **survivin, ovarian carcinoma, progression.**

Ovarian cancer occupies the place among the leading causes of death from gynecological cancer. Although the 5-year survival rate for all stages has improved recently, it is still disappointingly low (30%), largely because that there is no efficient methods for diagnosis and therapy [1]. So it is important to search for a biomarker identifying high risk patients.

Survivin is a member of the inhibitor of apoptosis protein (IAP) family and has been implicated in both apoptosis inhibition and cell cycle control [2, 3]. It is aberrantly expressed in various kinds of cancer cells but is undetectable in normal differentiated adult tissues, except testis, thymus, and placenta [4]. Moreover, many studies have reported that the expression rate of survivin in tumor tissues is associated with tumor progression and unfavorable clinicopathologic variables, such as poor prognosis, shorter patient survival rates and chemoresistance [5–12].

Survivin is expressed in human carcinomas, but its expression levels in tissues are different, that is associated with the poor outcome of patients [13–14]. Many studies have demonstrated that rate of expression and subcellular localization of survivin correlated with the progression and prognosis of ovarian carcinoma [15–18]. In this study, we used QRT-PCR to analyze survivin expression levels in benign ovarian tumors, ovarian carcinomas of different stages in order to identify these correlations. It was shown that the high survivin mRNA expression is implicated in ovarian carcinoma progression and may serve as a prognostic marker for ovarian carcinoma patients.

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Abbreviations used: IAP – inhibitor of apoptosis protein; MDS – myelodysplastic syndrome; QRT-PCR – quantitative real-time PCR; RT-PCR – reverse transcription-polymerase chain reaction.

MATERIALS AND METHODS

Patients and tissue handling. Fresh ovarian tissues were obtained with Institutional Review Board approved informed consent from patients treated by the Department of Gynecologic & Obstetrics at Qilu hospital of Shandong University between December 2005 and July 2006, and include 63 cases of ovarian carcinoma, 19 cases of borderline ovarian carcinoma, 21 cases of benign ovarian tumor, and 11 samples of normal ovarian tissue from patients who underwent total abdominal hysterectomy with salpingo-oopherectomy for non-malignant gynecologic disease. The patients ranged in age from 19 to 72 years (51.3 ± 19.6 years; median age, 56 years). The staging and grading of tumors were determined in accordance with the International Federation of Gynecology and Obstetrics (FIGO) criteria (1985) for malignant ovarian carcinoma; 28 tumors were classified as early stage (I/II) and 35 — as advanced stage (III/IV); 30 cases were at low grade (G1–G2), and 33 — at high grade(G3). Histological types included serous (n = 42), mucinous (n = 12), and endometrioid (n = 9). There were 34 cases with lymph node metastasis and 36 cases with ascites. All tissue specimens were immediately frozen in liquid nitrogen and then stored in –80 °C until use.

RNA extraction and reverse transcription. Total RNA was extracted from frozen tissues by the Trizol reagent (Invitrogen, USA), according to the supplier's

protocol. Total RNA (3 μg) samples were reverse transcribed to a final volume of 20 μl, using 50 pM oligo-(dT)-primer (TaKaRa, Japan), 1 mM dNTP mix (TaKaRa, Japan), 200 U reverse transcriptase (Promega, USA), and 5 × buffer 4 μl. RT reactions were performed on Mastercycler (Eppendorf, Germany). RNA was treated for 30 min at 37 °C by DNase before reverse transcription.

RT-PCR analysis survivin mRNA expression in ovarian tissues. We screened the positive expression of survivin mRNA by RT-PCR in 114 ovarian samples. The cDNA was amplified in a 25 μl reaction volume containing 1 U Taq polymerase (Promega, USA), 100 μM dNTP, 1.5 mM $MgCl_2$, 5 μl 10 × polymerase chain reaction buffer, and 50 mM KCL. Specific primers for survivin and β-actin were generated using the Primer 3 software and prepared by Invitrogen Biotech. The sequences of the primers are shown in Table 1. All PCRs were performed by Mastercycler (Eppendorf, Germany). The cycling conditions comprised a denaturation step for 5 min at 95 °C, followed by 40 cycles of denaturation (95 °C for 30 s), annealing (53 °C for 30 s) and extension (72 °C for 30 s). The PCR products were electrophoresed on a 2% agarose gel, stained with ethidium bromide (0.5 μg/ml), and visualized by an UV transilluminator (Alpha Innotech, USA).We used human β-actin as an internal marker. It was considered positive if PCR product was 110 bp by gel electrophoresis.

Table 1. Primers used for PCR

Survivin	Antisense sense	CTTTCTCAACGACCACCG GTAGGTGACGGGGTGAC	110 bp	NM001168.2
β-Actin	Antisense sense	GTTGCGTTACACCCTTTC CTGTCACCTTCACCGTTC	152 bp	NM001101.2

QRT-PCR analysis survivin mRNA expression levels in ovarian tisssues. QRT-PCR was used to determine relative survivin mRNA expression levels in 59 cases with survivin (+) ovarian tissues. QRT-PCR analysis was performed on Light Cycler (Roche Applied Science, USA) and on a volume of 20 μl containing 1 μl of cDNA, 10 μl of 10 × SYBR Green PCR Master Mix (TaKaRa, Japan), 0.5 μl of each primer (10 pM), and 8 μl of DEPC-treated water. Primers for survivin and β-actin were same as those used for RT-PCR. The program for detection survivin was set at 95 °C for 10 s, quantification program (95 °C for 0 s, 56 °C for 5 s, and 72 °C for 1 s, 83 °C for 1 s) which was repeated 55 times, a melting curve program (95 °C for 0 s and 65°C for 30 s, 95°C with a heating rate of 0.1 °C for 1 s and continuous fluorescence measurement), and a cooling step to 40 °C for 30 s. The program for detected β-actin was set at 95 °C for 10 s, quantification (95 °C for 0 s, 53 °C for 5 s, and 72 °C for 10 s) which was repeated 55 times, a melting curve program (95 °C for 0 s and 65 °C for 30 s, 95 °C with a heating rate of 0.1 °C for 1 s and continuous fluorescence measurement), and a cooling step to 40 °C for 30 s. A standard curve of cycle thresholds using serial dilutions of cDNA samples were used to calculate the relative abundance. Melting curve analysis was performed to confirm production of a single product in each reaction. The specificity of the amplification products was verified further by subjecting the amplification products to electrophoresis on a 2% agarose gel. Survivin mRNA expression was normalized to the expressed housekeeping gene β-actin. The data was analyzed with Light Cycle software 4.0 (Roche Applied Science, USA).

Statistical analysis. All statistical analyses were performed with the SPSS 11.5 J software package for Windows (SPSS Inc, Chicago, IL). The correlation between survivin expression and clinicopathologic features was statistically analyzed with the Chi-square test and Fisher's exact test. Student's two-tailed *t*-test was used to compare data between two groups. One-way analysis of variance and Bonferroni's correction were used to compare data between three or more groups. *P*-value < 0.05 was considered statistically significant.

RESULTS

RT-PCR analysis survivin mRNA expression in ovarian tissues. RT-PCR analysis showed that there were 59 cases with positive survivin mRNA expression from 114 ovarian tissue samples, including zero in normal ovarian tissues, 46 (73%) in the 63 cases of ovarian carcinomas, 8 (47%) in the 19 cases of borderline ovarian carcinomas, 4 (19%) in 21 cases of benign ovarian tumors (Table 2, Fig. 1, Fig. 2, *a*). The data on relationship between the various clinicopathologic features and survivin mRNA expression rate are described in Table 2. A significant positive correlation ($P = 0.026$) was observed between survivin mRNA expression rate and histological grade (Fig. 2, *b*). Of the 30 low-grade (G_1–G_2) tumors, 18 (60%) showed survivin mRNA expression. In contrast, 25 (84%) of 33 high-grade tumors (G_3) were positive for survivin mRNA expression. Furthermore, a significant correlation ($P = 0.049$) became evident between survivin expression and clinical stage of the disease (Fig. 2, *c*). 17 (60%) cases with positive survivin expression were related to stage I/II, and 29 (82%) cases to stage III/IV. The survivin expression rate in ovarian carcinomas was associated with histological type ($P = 0.008$, Fig. 2, *d*), but no correlation was found between survivin expression and lymph node metastasis ($P = 0.921$, Fig. 2, *e*) or ascites ($P = 0.87$, Fig. 2, *f*) .

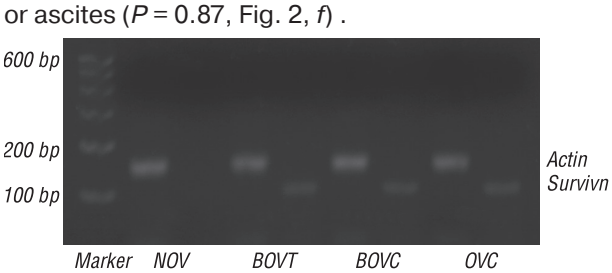

Fig. 1. Survivin mRNA expression in ovarian tissues analyzed by RT-PCR. NOV: normal ovarian carcinoma, BOVT: benign ovarian tumor, BOVC: borderline ovarian carcinoma, OVC: ovarian carcinoma. Actin — 152 bp, survivin — 110 bp

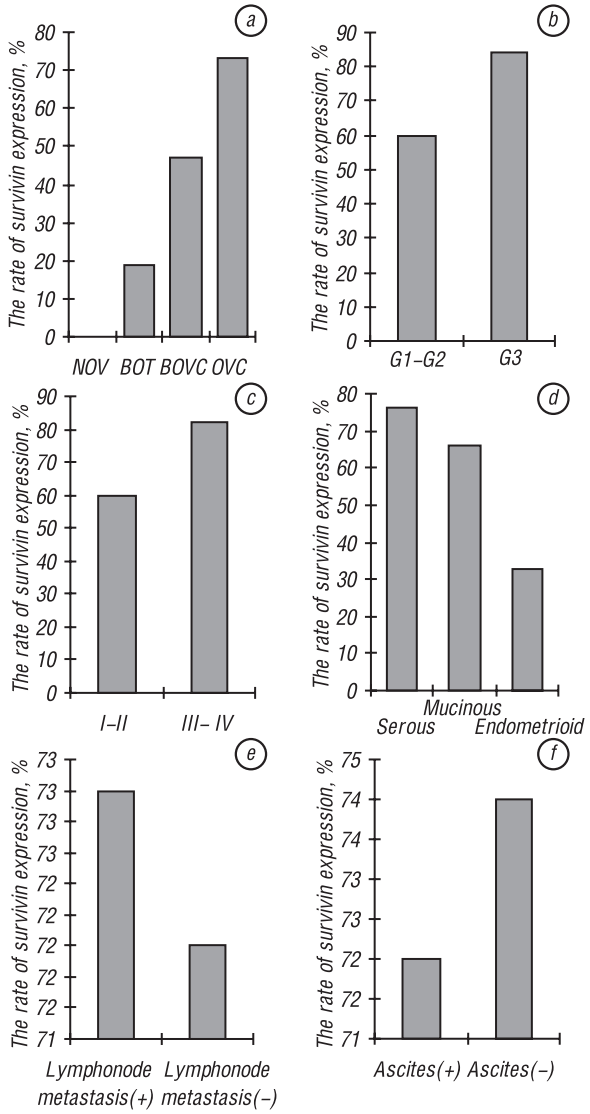

Fig. 2. The rate of survivin expression in ovarian tissue samples dependent on type of tumor (*a*) NOV: normal ovarian carcinoma, BOVT: benign ovarian tumor, BOVC: borderline ovarian carcinoma, OVC: ovarian carcinoma); differentiation grade (*b*); clinical stage (*c*); histological type (*d*); lymph node metastasis (*e*) and ascites (*f*)

Table 2. Expression of survivin mRNA in ovarian tissue samples

Sample	Number of patients	Positive survivin expression (%)	*P*-value
Normal ovarian tissue	11	0 (0%)	
Benign ovarian tumor	21	4 (19%)	
Borderline ovarian carcinoma	19	9 (47%)	
Ovarian carcinoma	63	46 (73%)	
Grade:			0.026
G1–G2	30	18 (60%)	
G3	33	28 (84%)	
FIGO stage:			
I–II	28	17 (60%)	0.049
III–IV	35	29 (82%)	
Histological type:			
serous	42	35 (76%)	0.008
mucinous	12	8 (66%)	
endometrioid	9	3 (33.3%)	
Lymph node metastasis:			0.921
Yes	34	25 (73%)	
No	29	21 (72%)	
Ascites:			0.87
yes	36	26 (72%)	
No	27	20 (74%)	

QRT-PCR analysis survivin mRNA expression levels. QRT-PCR was used to determine relative expression levels of the survivin gene in 59 cases with survivin (+) ovarian tissues. The results demonstrated that higher levels of survivin/β-actin mRNA expression in ovarian carcinoma (0.0122 ± 0.00486) than that in borderline ovarian carcinoma tissues (0.0055 ± 0.00188) and benign ovarian tumor tissues (0.0007 ± 0.00011). There was statistical difference among them ($P < 0.01$, Fig. 3, *a*). The results also demonstrated that there was significant difference of mean survivin/ β-actin mRNA expression levels between G_1–G_2 and G_3 in ovarian carcinoma (0.0104 ± 0.00348 versus 0.0142 ± 0.00533, $P = 0.041$, Fig. 3, *b*). In advanced stage (III/IV) cancers, the mean survivin/β-actin mRNA expression levels were higher than that in early-stage (I/II) cancers (0.0104 ± 0.00316 versus 0.0141 ± 0.00537, $P = 0.041$, Fig. 3, *c*). Furthermore, we found that the mean survivin mRNA levels were higher in cases with lymph node metastasis than that without lymph node metastasis (0.0103 ± 0.00302 versus 0.0144 ± 0.00546, $P = 0.031$, Fig. 3, *d*). No statistical difference ($P > 0.05$, Fig. 3, *e*) was identified in survivin expression among serous cancers, endometrioid and mucinous, no statistic difference ($P > 0.05$, Fig. 3, *f*) to ascites either (Table 3).

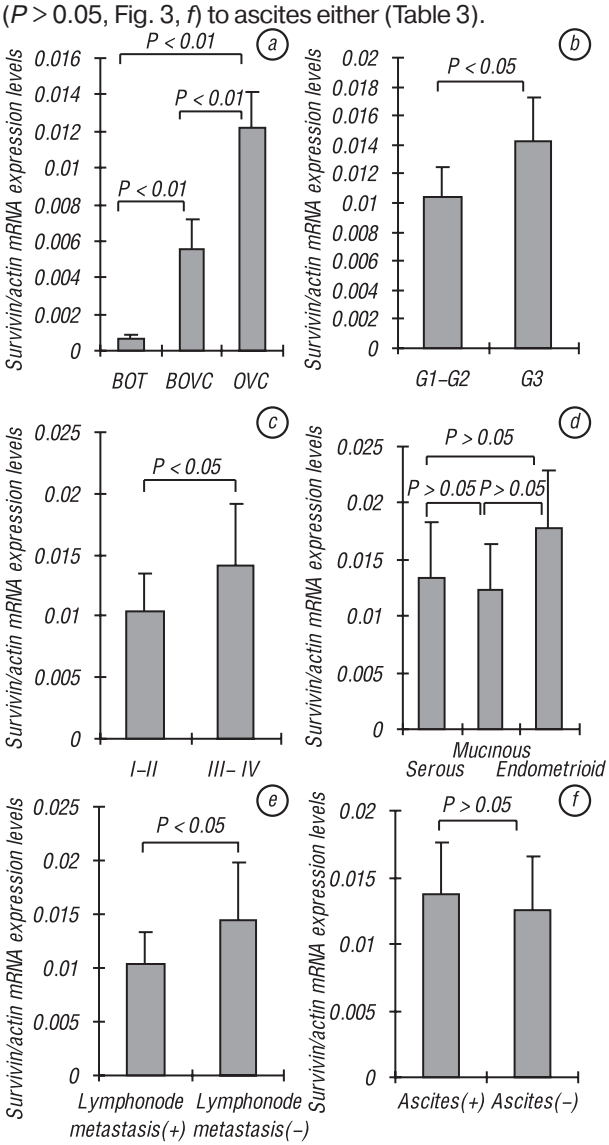

Fig. 3. Survivin/actin mRNA expression levels in ovarian tissues measured by real time PCR depenedent on on type of tumor (*a*) NOV: normal ovarian carcinoma, BOVT: benign ovarian tumor, BOVC: borderline ovarian carcinoma, OVC: ovarian carcinoma); differentiation grade (*b*); clinical stage (*c*); histological type (*d*); lymph node metastasis (*e*) and ascites (*f*)

Table 3. Survivin/β-actin mRNA expression levels

Sample	Survivin/β-actin mRNA expression levels (means ± SD)	*P*-value
Benign ovarian tumor	0.0007 ± 0.00011	
Borderline ovarian carcinoma	0.0055 ± 0.00188	< 0.001
Ovarian carcinoma	0.0122 ± 0.00486	
Grade:		
G1–G2	0.0104 ± 0.00348	0.041
G3	0.0142 ± 0.00533	
FIGO stage:		
I–II	0.0104 ± 0.00316	0.041
III–IV	0.0141 ± 0.00537	
Histological type:		
serous	0.0133 ± 0.00525	0.673 (s vs m)
mucinous	0.0123 ± 0.00478	0.600 (s vs e)
endometrioid	0.0177 ± 0.00562	0.856 (m vs e)
Lymphonode metastasis:		
Yes	0.0103 ± 0.00302	0.031
No	0.0144 ± 0.00546	
Ascites:		
yes	0.0137 ± 0.00518	
no	0.0125 ± 0.00526	0.563

DISCUSSION

Ovarian carcinoma is among the most common female cancers and the leading cause of death from gynecologic malignancy in the world. Although the clinical and histological prognostic factors (e. g. tumor grade and clinical stage) had been reported to be of prognostic significance in ovarian cancer [19], it is conceivable that the assessment of biochemical factors more strictly related to tumor cell biology and intrinsic aggressiveness could help identifying high-risk patients and facilitating management of this disease.

Cell proliferation and cell death pathways meet at a pivotal crossroad, crucial to maintain normal homeostasis and to eliminate dangerous cells before they start dividing. Survivin is an intriguing and fascinating protein at this crossroad that interfaces life and death, through its dual role in facilitating cell division and encountering apoptosis [20]. Survivin promotes cell proliferation and enhances angiogenesis, it may play an important role in protecting abnormal cells from apoptosis during cell division, which contributes to tumor development and prognosis [21–23].

Several studies had shown that survivin mRNA expression levels correlated with the prognosis in such carcinomas as osteosarcoma and myelodysplastic syndrome [13–14]. Only the expression rate of survivin has been reported to be associated with progress and prognosis of ovarian carcinoma in some literatures [15–18], but little is known about the relationship between the expression levels of survivin and prognosis of ovarian carcinoma.

In our experiment we testified that the rate of survivin expression is associated with progression of ovarian carcinoma and some other parameters (FIGO stage, differentiation grade, and histological type). Moreover, we found that survivin expression levels were different in survivin positive tissues. Survivin expression levels were the highest in ovarian carcinomas, and there were the lowest survivin expression levels in benign ovarian tumor tissues. Furthermore, survivin expression levels are associated with the FIGO stage, grade, and lymph node metastasis, but not with ascites and histological type in ovarian carcinoma.

In this study we determined not only whether survivin gene was expressed or not, but also the levels of survivin expression in ovarian carcinoma. One can use real time PCR to detect the mRNA expression of ovarian tissues by biopsy. Furthermore, survivin is under study as a novel target for the treatment of cancer, and its expression may be regulated by different approaches [24–26].

The relationships between survivin expression levels and the survival rate or the reaction to chemotherapy of patients with ovarian carcinoma were not showed in the present study, because of the lack of the follow-up. Further long-term follow-up studies would be done in future to address these questions.

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ЭКСПРЕССИЯ СУРВИВИНА В ТКАНИ ПРИ РАКЕ ЯИЧНИКА

Цель: **исследовать экспрессию сурвивина в доброкачественных и злокачественных новообразованиях яичника.** ***Методы:*** **экспрессия мРНК сурвивина исследована методом RT-PCR в 114 образцах ткани яичника человека. Для установления уровня экспресии мРНК сурвивина применяли количественный PCR в режиме реального времени.** ***Результаты:*** **экспрессия мРНК сурвивина не выявлена в образцах нормальной ткани яичника, но зарегистрирована в 73% случаев рака яичника, 47% случаев серозных опухолей яичника серозного типа и 19% образцов доброкачественных опухолей. Установлена положительная зависимость между уровнем экспрессии мРНК сурвивина и клинической стадией заболевания ($P = 0{,}026$), и степенью дифференцировки опухоли ($P = 0{,}049$). Выявлена статистически значимая зависимость уровня экспрессии мРНК сурвивина от гистологического типа опухоли (серозного, мукозного, эндометриоидного, $P = 0{,}008$) и отсутствие таковой от наличия метастазов в лимфатических узлах ($P = 0.921$) или асцита ($P = 0.87$). Также установлено, что средние уровни экспрессии мРНК сурвивина выше при раке яичника, чем в ткани доброкачественных новообразований или серозных опухолей яичника пограничного типа ($P < 0{,}001$). При раке яичника высокий уровень экспрессии мРНК сурвивина коррелировал с клинической стадией заболевания, степенью дифференцировки опухолевых клеток, но не коррелировал с гистологическим типом новообразования.** ***Выводы:*** **результаты свидетельствуют о том, что экспрессия сурвивина ассоциирована с прогрессией рака яичника.**

Ключевые слова: **сурвивин, рак яичника, опухолевая прогрессия.**