ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Survivin expression at the mRNA level in tumors and the protein concentration in the serum and peritoneal fluid in patients with serous ovarian tumors

Authors: Celina Kruszniewska-Rajs, Marta Smycz-Kubanska, Barbara Strzalka-Mrozik, Jaroslaw Strzelczyk, Wojciech Szanecki, Andrzej Witek, Joanna Gola, Aleksandra Mielczarek-Palacz

DOI: 10.5603/GP.a2022.0158

Article type: Research paper

Submitted: 2022-07-08

Accepted: 2022-11-30

Published online: 2023-01-20

ORIGINAL PAPER / GYNECOLOGY

Survivin expression at the mRNA level in tumors and the protein concentration in the serum and peritoneal fluid in patients with serous ovarian tumors

Short title: Survivin level in patients with ovarian cancer

Celina Kruszniewska-Rajs[1], Marta Smycz-Kubanska[2], Barbara Strzalka-Mrozik[1], Jaroslaw Strzelczyk[2], Wojciech Szanecki[3], Andrzej Witek[3], Joanna Gola[1], Aleksandra Mielczarek-Palacz[2]

[1]Department of Molecular Biology, Faculty of Pharmaceutical Sciences in Sosnowiec Medical University of Silesia, Katowice, Poland

[2]Department of Immunology and Serology, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland

[3]Department of Gynecology and Obstetrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

Corresponding author:

Celina Kruszniewska-Rajs

Department of Molecular Biology, Faculty of Pharmaceutical Sciences in Sosnowiec Medical University of Silesia, Katowice, Poland

e-mail: ckruszniewska@sum.edu.pl

ABSTRACT

Objectives: Ovarian cancer is one of the gynecological cancers that have the worst prognosis. The expression of the proteins from the IAP family (inhibitor of apoptosis protein), including survivin, is observed in many types of cancer.

The aim of the study was to evaluate survivin at the mRNA level in tumors and the protein concentration in the serum and peritoneal fluid of patients with serous ovarian cancer in order to assess the relationship between the concentration of survivin and the histological subtypes of cancer.

Material and methods: The study group consisted of 55 women, including patients with serous ovarian cancer (n = 30, nine low-grade serous carcinoma LGSC, 21 high-grade serous carcinoma HGSC), serous cysts (n = 10) and the control group (n = 15). The concentration of protein in the peritoneal fluid and serum was assessed using ELISA tests. The expression of survivin gene *BIRC5* in the tumors was assessed using the RT-qPCR method.

Results: The data that was obtained indicated that the concentration of survivin was higher in the serum of the women with serous ovarian cancer compared those that had benign tumors ($p < 0.05$) and the control group ($p < 0.001$). The survivin concentration was also higher in both the serum and peritoneal fluid in the HGSC group compared to the LGSC group ($p < 0.001$). The mRNA level was highest in the HGSC group, and there was a statistically significant difference compared to those in the benign tumor group and HGSC group ($p < 0.05$).

Conclusions: The observed changes prove that the expression level increases significantly in HGSC in both the protein and mRNA levels. Based on these findings, it can be assumed that assessing this parameter could be a useful additional indicator of the progression and differentiation of this type of cancer. However, this requires further research in a larger group of patients and possibly in other types of ovarian cancer

Key words: ovarian cancer; survivin; molecular marker; gene expression

INTRODUCTION

Ovarian cancer is one of the gynecological cancers that have the worst prognosis and the highest mortality. According to statistical analyses, mortality from this disease will increase significantly by 2040 [1]. This is primarily due to the lack of characteristic clinical symptoms in the initial stage of the disease and the lack of diagnostic tests that can detect a tumor at an early stage of its clinical advancement [2, 3]. The impaired immune responses against cancer cells play an important role in the pathogenesis of ovarian cancer *via* apoptosis [4]. Currently, research is being conducted whose goal is to understand the role of the proteins belonging to the IAP (Inhibitor of Apoptosis Protein) family, one of which is survivin [5, 6].

Survivin is a protein that is composed of 142 amino acids, and unlike the other members of the IAP family, it contains a single Baculovirus Inhibitor of Apoptosis Protein Repeat (BIR) domain, which is responsible for anti-apoptotic properties [7]. This protein is encoded by the *BIRC5* gene, which is located on chromosome 17 (17q25), the transcription of which leads to the formation of 431 bp survivin mRNA [8]. Five isoforms of the human survivin gene transcript have been found to encode the following proteins: survivin, survivin 2A,

survivin 2B, survivin ΔEx3 and the most common — survivin 3B [9]. Survivin is involved in the regulation of the cell cycle and programmed cell death. During mitosis, it is responsible for the correct localization of the Chromosomal Passenger Complex (CPC) around the chromosomal centromeres and for the stabilization of the karyokinetic spindle microtubules. In the process of apoptosis, it participates in the inhibition of caspase activity and in the inactivation of Mitochondrial Apoptosis-Inducing Factor (AIF) and Second Mitochondria-Derived Activator of Caspases (Smac/DIABLO) [8]. In response to the cell death-inducing factors, the mitochondrial survivin levels decrease, and this protein is released into the cytoplasm and prevents caspase activation, thereby inhibiting apoptosis. It also plays an interesting role in another type of cell death, autophagy. A decrease in the protein content in cells may induce apoptosis *via* an autophagy-dependent mechanism that involves its regulator — beclin 1 protein [10].

The unique function of survivin in the pathogenesis of cancer is worth noting; in during the initiation, progression, and metastasis, and due to the high expression of this protein in cancer cells, much attention is now being paid to the possibility of using survivin as a diagnostic or prognostic factor [11–13]. Its increased expression may result from the amplification of the survivin locus on chromosome 17q25, exon DNA demethylation, increased gene promoter activity, or the upregulation of the phosphatidylinositol-3-kinase (PI3K) signaling pathways and mitogen-activated protein kinases (MAPK) [14, 15].

To date, the studies that have been conducted on using survivin in the diagnosis and treatment of the ovarian cancer diseases have not provided unequivocal results; thus, there is a need to conduct further research on the biology of this cancer in order to develop new diagnostic and therapeutic strategies.

Therefore, the aim of the study was to evaluate survivin in serous ovarian tumors at the mRNA level, to analyze the concentration of survivin in the serum and peritoneal fluid of patients with serous ovarian cancer, and to determine whether there is a relationship between the concentration of survivin and the histological subtypes of this cancer.

MATERIAL AND METHODS

The study group consisted of 55 women, age 19–82 (median — 60, Q-47, Q3-68), including patients with diagnosed ovarian cancer (n = 30), benign lesions (n = 10) and the control group (n = 15). The group of women with ovarian cancer included patients who had been diagnosed with *Cystadenocarcinoma papillare serosum IIIC* (tumor advancement was determined according FIGO classification — International Federation of Gynecology and Obstetrics). Among this group, nine tumors were classified as low-grade serous carcinoma

(LGSC) and 21 tumors were classified as high-grade serous carcinoma (HGSC). The benign tumor group consisted of samples from ten patients with serous ovarian cysts (Cystadenoma serosum). The control group consisted of 15 healthy women in whom no pathological changes were detected within the reproductive system. Patients were hospitalized at Department of Gynecology and Obstetrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia and the Department of Gynecological Oncology of the Provincial Specialist Hospital in Częstochowa. The women who participated in the study consented to conducting the research. The approval of the Ethics Committee of the Medical University of Silesia in Katowice was obtained.

Qualification of patients to the appropriate study groups was based on the tests that were performed, including a gynecological examination and transvaginal ultrasound. If a patient was diagnosed with an ovarian tumor, computed tomography was additionally performed to confirm the diagnosis. The type of the examined tumors was additionally confirmed by a histopathological diagnosis. The exclusion of any pathologies in the female genital tract enabled the patients to be qualified in the control group.

The material for the ovarian cancer group consisted of the serum, peritoneal fluid and a fragment of the cancer tumor, for benign tumor group — the serum and a fragment of the tumor were examined. Blood was drawn from the women with ovarian tumors before the surgery. The peritoneal fluid and fragment of the tumor were collected during the surgery. Blood samples for the control group were drawn during their periodic pelvic examination.

The concentration of protein in the peritoneal fluid and serum was assessed using the enzyme-linked immunosorbent assay (ELISA). The tests were performed using the Elisa test for survivin (Cloud Clone Corp., Katy, TX, USA), the sensitivity of which was 11.7 pg/mL.

Total RNA was extracted from the tissue using a Trizol reagent and were then used in a RT-qPCR reaction to determine the *BIRC5* mRNA level. The reaction was performed using the GoTaq 1-Step RT-qPCR System (Promega, Waldorf, Germany) and a LightCycler 480 System (Roche, Basel, Switzerland). The relative quantification method $2^{-\Delta Ct}$ was used to determine the expression level of *BIRC5* mRNA with *β-actin* as the reference gene [16, 17].

The results were statistically analyzed using Statistica 13.3 software. The normality of the distribution of the studied variables was assessed using the Shapiro-Wilk test. The median and interquartile ranges were determined for the parameters that were tested, and the obtained results were compared using the Mann-Whitney and Kruskal-Wallis tests. The analysis found that $p < 0.05$ was considered the statistically significant level.

RESULTS

The concentration of survivin was determined in the serum of the women from the control group, those with benign tumors (*Cystadenoma serosum*) and serous ovarian cancer (*Cystadenocarcinoma serosum IIIC*).

In the serum of the control group, the concentration of survivin was below the sensitivity threshold of the test, which was 11.7 pg/mL. The concentration of the parameter being studied varied depending on the clinical diagnosis of the tumor. The highest concentrations were found in the serum of the women with ovarian cancer, in which Q1 and Q3 were 9.21 and 221.05, respectively (median 81.57 pg/mL).

However, in the group of women with benign tumor-ovarian cysts, Q1 and Q3 were 0.00 and 51.11, respectively, with a median of 9.62 p/mL. A statistically significantly higher concentration of the examined parameter was found in the serum of the women with cancer compared to the concentration in the women in the control group ($p < 0.01$). Moreover, the performed statistical analysis showed that the concentration of survivin was higher in the serum of the women with serous ovarian cancer compared to the concentration in the serum of the patients with benign tumors ($p < 0.05$). The obtained results are presented in Figure 1 and Table 1.

In the peritoneal fluid of the women with ovarian cancer, Q1 and Q3 were 32.03 and 245.01, respectively (median 107.27 pg/mL). No statistically significant differences were found in the serum in the ovarian cancer group compared to the concentration in the peritoneal fluid as is shown in Figure 2.

A further analysis included an assessment of the survivin concentration that was dependent on the degree of the histological differentiation of cancer, both in the serum and in the peritoneal fluid.

The analysis showed a statistically significant difference between the control group and HGSC and between LGSC and HGSC ($p < 0.001$) ── Figure 3 and Table II. In the peritoneal fluid of the women with ovarian cancer, there was a statistically significant difference between LGSC and HGSC ($p < 0.001$) ── the obtained results are presented in Figure 4.

Changes in the expression of the *BIRC5* mRNA level in the women with ovarian cancer or a benign tumor are presented in Figure 5. An analysis showed a statistically significant difference between the benign tumor group and HGSC ($p < 0.05$). There was no statistical significance between LGSC and HGSC (Tab. 3).

DISCUSSION

There is evidence that the proteins that are involved in programmed cell death are important in tumor progression. It also appears that apoptosis inhibiting proteins performing additional functions in other cellular processes may act as oncogenes and that increasing their expression might potentially promote tumor formation [18]. This process is extremely complex, and apoptotic disorders are one of its most important stages. Currently, research is being conducted to understand the role of the proteins belonging to the family of apoptosis inhibitors, including survivin, which, due to its high expression level in tumor cells, is being investigated in terms of its possible use in the diagnosis and therapy of ovarian cancer.

To date, most of the research on the role of survivin in the formation and development of ovarian tumors has focused on the assessment of tissue expression using the immunohistochemical method. The expression of survivin in ovarian cancer cells using the immunohistochemical method in patients who were being treated for primary epithelial ovarian malignancies with different degrees of histological maturity and clinical advancement was assessed by Nowak-Markwitz et al. [19]. The conducted studies showed that the survivin expression correlated with the degree of the histological maturity of the tumor.

Similar studies were conducted by Plewka et al. [20], who also assessed the survivin expression in tissue sections of epithelial ovarian tumors using immunohistochemistry. In the group of serous tumors, the expression of survivin was detected in 24.0% of the cases with benign tumors, in 60.0% of the cases with borderline tumors and in 91.0% of the cases with ovarian cancer. In mucous tumors, the survivin expression was shown in 33.5% of the cases with benign tumors, in 43.5% of the cases with borderline tumors, and in 80% of the cases with malignant tumors. According to the authors, an overexpression of survivin could play a key role in the development of ovarian epithelial tumors in women and may have an important prognostic value in patients with epithelial ovarian cancer.

Turan et al. [21] assessed the expression of survivin in tissue sections of patients with serous ovarian cancer. The research included patients with benign, borderline and malignant tumors. The conducted studies showed that the survivin expression was significantly higher in the tissues of the malignant tumors compared to the borderline lesions and benign tumors. Moreover, the conducted studies showed the existence of a statistically significant relationship between an increase in the survivin expression and an increase in the clinical advancement according to the FIGO and the histological maturity of the tumor.

A study evaluating survivin using immunohistochemistry in a group of patients with mucous tumors was conducted by Kanter et al. [22]. The study included a group of patients with benign tumors, borderline lesions and cancer. The highest expression of survivin was found in the patients with ovarian cancer and it was statistically significantly higher than in the other groups. It was also found that the increased expression of survivin showed a statistically significant correlation between an increase in the clinical advancement of the cancer, the degree of the histological maturity of a tumor and the presence of lymph node metastases.

Kucukgoz-Gulec et al. [23], who also used the immunohistochemical method to study the survivin expression in tissue sections from patients with diagnosed epithelial ovarian cancer obtained different results. The conducted studies showed the expression of survivin in 20% of the patients with ovarian cancer. No relationship was observed between the survivin expression and the degree of the histological maturity of a tumor, the histotype of ovarian cancer, or a resistance to treatment with platinum compounds.

Because the changes that are associated with soluble mediators of the apoptosis process that accompanies ovarian tumors are still not fully understood, further research is required.

Our research was based on the analysis of the results that were obtained for tumors and benign cysts. The premise for selecting such a study group was the fact that *Cystadeno-carcinoma papillare serosum IIIC* and serous ovarian cysts *(Cystadenoma serosum)* are the most common diagnoses in patients. In addition, limiting the type of tumor and cyst enabled a homogeneous study group to be created. The obtained results showed that the concentration of survivin was significantly higher in the serum of the women with serous ovarian cancer compared to the concentration in the serum of the women with an ovarian cyst and those in the control group, which indicates disturbances in the apoptosis process that involves survivin, which may be one of the most important immune mechanisms that contributes to the development of this type of tumor. Interesting observations were also provided by the analysis of the concentration of survivin in the peritoneal fluid of the women with ovarian cancer. The concentration of survivin was slightly higher in the peritoneal fluid compared to that in the serum, which indicates an intensification of the changes in the peritoneal fluid environment of a tumor with the participation of the studied protein. Moreover, a statistically significant correlation was demonstrated between the concentration of the tested protein in both the serum and peritoneal fluid and the degrees of the histological differentiation of the cancer, which indicates a relationship between survivin secretion and the histological differentiation of

cancer that in the future might prove useful in the development of new diagnostic and therapeutic strategies.

Similar studies were conducted by Dobrzycka et al. [24], who assessed the concentration of survivin in the blood serum of women with diagnosed serous ovarian cancer. As a result of the conducted research, it was shown that the concentration of survivin in the blood serum of the women with ovarian cancer was significantly higher than the concentration in the serum of the healthy women who constituted the control group. Moreover, it was shown that an increase in the survivin concentration positively correlated with an increase in the clinical stage of cancer according to the FIGO, an increase in the histological malignancy of a tumor, the presence of ascites and the level of cytoreduction. According to the authors, determining the serum survivin concentration might be helpful in the early detection of serous ovarian cancer and might provide important information about the prognosis in patients.

An analysis of the concentration of survivin in the blood serum of patients with ovarian cancer was also conducted by No et al. [25]. The study included patients with serous ovarian cancer, benign tumors as well as those with dermoid and endometrial cysts. As a result of the conducted studies, it was shown that in the serum of the patients with ovarian cancer, the concentration of survivin was higher than in the serum of the patients with benign tumors, and that it was strongly correlated with age, the disease severity and progression-free survival. According to the authors, serum survivin reflects the peritoneal metastasis of serous ovarian cancer and thus might be useful as a prognostic biomarker.

Gunaldi et al. [26] assessed the serum concentration of survivin in cancer patients in order to determine its diagnostic value. In addition, the authors also assessed the correlation between the serum survivin concentration and the clinical and pathological features of cancer patients. Patients with ovarian, breast, colon cancer and other tumors were qualified for the study. The conducted studies showed that the serum concentration of survivin in the cancer patients was significantly higher than in the healthy subjects. No significant relationships were found between the serum survivin level and the demographic characteristics of the cancer. According to the authors, survivin could be used as a marker that implies malignancy or as a marker for differential diagnosis of malignancy and other benign diseases, but this requires further research.

Interesting observations were provided by the studies conducted by He et al. [27], who assessed the clinical and pathological significance of survivin using a meta-analysis using PubMed, EMBASE, the Web of Science and the Cochrane Library. The meta-analysis

included twelve studies in 1,097 patients. Although the survivin overexpression was shown to be closely related to the FIGO stage of ovarian cancer, the degree of the histological differentiation of a tumor, no significant association with lymphatic metastases was shown. According to the authors, survivin might turn out to be a novel clinicopathological marker of ovarian carcinoma.

CONCLUSIONS

To summarize, the obtained results indicate an association between the level of survival expression and the progression of serous ovarian cancer *Cystadenocarcinoma papillare serosum IIIC*. Both the mRNA and protein levels were higher in a tumor compared to the control group and patients with a benign lesion. Additionally, an increase in expression was observed in HGSC — high-grade serous carcinoma. The performed study concerned only one type of ovarian neoplasm and one type of cyst, which is a reason to undertake research in other ovarian neoplasms in order to confirm the usefulness of the evaluation of the survivin level as an additional parameter in ovarian cancer diagnostics.

Funding

This research was funded by Medical University of Silesia in Katowice, Poland; grant number PCN-1-069/K/1/O.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Momenimovahed Z, Tiznobaik A, Taheri S, et al. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health. 2019; 11: 287–299, doi: 10.2147/IJWH.S197604, indexed in Pubmed: 31118829.

2. Stewart C, Ralyea C, Lockwood S. Ovarian cancer: an integrated review. Semin Oncol Nurs. 2019; 35(2): 151–156, doi: 10.1016/j.soncn.2019.02.001, indexed in Pubmed: 30867104.

3. Kujawa KA, Lisowska KM. [Ovarian cancer--from biology to clinic]. Postepy Hig Med Dosw (Online). 2015; 69: 1275–1290, doi: 10.5604/17322693.1184451, indexed in Pubmed: 26671919.

4. Binju M, Amaya-Padilla MA, Wan G, et al. Therapeutic inducers of apoptosis in ovarian cancer. Cancers (Basel). 2019; 11(11), doi: 10.3390/cancers11111786, indexed in Pubmed: 31766284.

5. Chandra A, Pius C, Nabeel M, et al. Ovarian cancer: Current status and strategies for improving therapeutic outcomes. Cancer Med. 2019; 8(16): 7018–7031, doi: 10.1002/cam4.2560, indexed in Pubmed: 31560828.

6. Denel-Bobrowska M, Marczak A. The role of survivin in the diagnosis and therapy of gynaecological cancers. Postepy Hig Med Dosw (Online). 2016; 70(0): 1182–1189, indexed in Pubmed: 28026821.

7. Nogueira-Ferreira R, Vitorino R, Ferreira-Pinto MJ, et al. Exploring the role of post-translational modifications on protein-protein interactions with survivin. Arch Biochem Biophys. 2013; 538(2): 64–70, doi: 10.1016/j.abb.2013.07.027, indexed in Pubmed: 23938875.

8. Athanasoula KCh, Gogas H, Polonifi K, et al. Survivin beyond physiology: orchestration of multistep carcinogenesis and therapeutic potentials. Cancer Lett. 2014; 347(2): 175–182, doi: 10.1016/j.canlet.2014.02.014, indexed in Pubmed: 24560928.

9. Waligórska-Stachura J, Andrusiewicz M, Sawicka-Gutaj N, et al. Evaluation of survivin splice variants in pituitary tumors. Pituitary. 2015; 18(3): 410–416, doi: 10.1007/s11102-014-0590-9, indexed in Pubmed: 25107550.

10. Wheatley SP. The functional repertoire of survivin's tails. Cell Cycle. 2015; 14(2): 261–268, doi: 10.4161/15384101.2014.979680, indexed in Pubmed: 25607650.

11. Jaiswal PK, Goel A, Mittal RD. Survivin: A molecular biomarker in cancer. Indian J Med Res. 2015; 141(4): 389–397, doi: 10.4103/0971-5916.159250, indexed in Pubmed: 26112839.

12. Garg H, Suri P, Gupta JC, et al. Survivin: a unique target for tumor therapy. Cancer Cell Int. 2016; 16: 49, doi: 10.1186/s12935-016-0326-1, indexed in Pubmed: 27340370.

13. Shojaei F, Yazdani-Nafchi F, Banitalebi-Dehkordi M, et al. Trace of survivin in cancer. Eur J Cancer Prev. 2019; 28(4): 365–372, doi: 10.1097/CEJ.0000000000000453, indexed in Pubmed: 29847456.

14. Cao XQ, Lu HS, Zhang L, et al. MEKK3 and survivin expression in cervical cancer: association with clinicopathological factors and prognosis. Asian Pac J Cancer Prev. 2014; 15(13): 5271–5276, doi: 10.7314/apjcp.2014.15.13.5271, indexed in Pubmed: 25040987.

15. Zhang Yi, Chen Hx, Zhou Sy, et al. Sp1 and c-Myc modulate drug resistance of leukemia stem cells by regulating survivin expression through the ERK-MSK MAPK signaling pathway. Mol Cancer. 2015; 14: 56, doi: 10.1186/s12943-015-0326-0, indexed in Pubmed: 25890196.

16. Livak K, Schmittgen T. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods. 2001; 25(4): 402–408, doi: 10.1006/ meth.2001.126.

17. Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc. 2008; 3(6): 1101–1108, doi: 10.1038/nprot.2008.73, indexed in Pubmed: 18546601.

18. Cetraro P, Plaza-Diaz J, MacKenzie A, et al. A review of the current impact of inhibitors of apoptosis proteins and their repression in cancer. Cancers (Basel). 2022; 14(7), doi: 10.3390/cancers14071671, indexed in Pubmed: 35406442.

19. Nowak-Markwitz E, Puła B, Szajnik M, et al. [Expression of survivin, SDF-1 and CXCR4 on tumor cells in ovarian cancer]. Ginekol Pol. 2010; 81(9): 674–677, indexed in Pubmed: 20973204.

20. Plewka D, Jakubiec-Bartnik B, Morek M, et al. Survivin in ovary tumors. Ginekol Pol. 2015; 86(7): 525–530, doi: 10.17772/gp/57855, indexed in Pubmed: 26376531.

21. Turan G, Usta CS, Usta A, et al. The expression of HER-2/neu (c-erbB2), survivin and cycline D1 in serous ovarian neoplasms: their correlation with clinicopathological variables. J Mol Histol. 2014; 45(6): 679–687, doi: 10.1007/s10735-014-9591-2, indexed in Pubmed: 25106503.

22. Kanter M, Turan G, Usta C, et al. Survivin and cycline D1 expressions are associated with malignant potential in mucinous ovarian neoplasms. J Mol Histol. 2016; 47(2): 145–152, doi: 10.1007/s10735-016-9661-8, indexed in Pubmed: 26815661.

23. Kucukgoz Gulec U, Gumurdulu D, Guzel AB, et al. Prognostic importance of survivin, Ki-67, and topoisomerase IIα in ovarian carcinoma. Arch Gynecol Obstet. 2014; 289(2): 393–398, doi: 10.1007/s00404-013-3000-z, indexed in Pubmed: 23974278.

24. Dobrzycka B, Mackowiak-Matejczyk B, Terlikowska KM, et al. Prognostic significance of pretreatment VEGF, survivin, and Smac/DIABLO serum levels in patients with serous ovarian carcinoma. Tumour Biol. 2015; 36(6): 4157–4165, doi: 10.1007/s13277-015-3050-x, indexed in Pubmed: 25577253.

25. No JH, Jeon YT, Kim YB, et al. Quantitative detection of serum survivin and its relationship with prognostic factors in ovarian cancer. Gynecol Obstet Invest. 2011; 71(2): 136–140, doi: 10.1159/000316049, indexed in Pubmed: 21160138.

26. Gunaldi M, Isiksacan N, Kocoglu H, et al. The value of serum survivin level in early diagnosis of cancer. J Cancer Res Ther. 2018; 14(3): 570–573, doi: 10.4103/0973-1482.171369, indexed in Pubmed: 29893319.

27. He X, Yang K, Wang H, et al. Expression and clinical significance of survivin in ovarian cancer: A meta-analysis. PLoS One. 2018; 13(5): e0194463, doi: 10.1371/journal.pone.0194463, indexed in Pubmed: 29795564.

Table 1. Statistical analysis of the survivin concentration in the serum of the patients with serous ovarian cancer, an ovarian cyst and the control group

	Serous ovarian	**Ovarian cyst**	**Control group**

	cancer		
Serous ovarian cancer		p = 0.024677	p = 0.000613
Ovarian cyst	p = 0.024677		NS
Control group	p = 0.000613	NS	

NS — no statistical significance

Table 2. Statistical analysis of the concentration in the serum of the patients with ovarian cancer depending on the degree of differentiation and control group

	LGSC	HGSC	Control group
LGSC		0.000644	NS
HGSC	0.000644		1. 000011
Control group	NS	0.000011	

HGSC — high-grade serous carcinoma; LGSC — low-grade serous carcinoma; NS — no statistical significance

Table 3. Statistical analysis of mRNA *BIRC5* expression in an ovarian cyst or a cancer tumor depending on the degree of differentiation

	LGSC	**HGSC**	**Ovarian cyst**
LGSC		NS	NS
HGSC	NS		0.009834
Ovarian cyst	NS	0.009834	

HGSC — high-grade serous carcinoma; LGSC — low-grade serous carcinoma; NS — no statistical significance

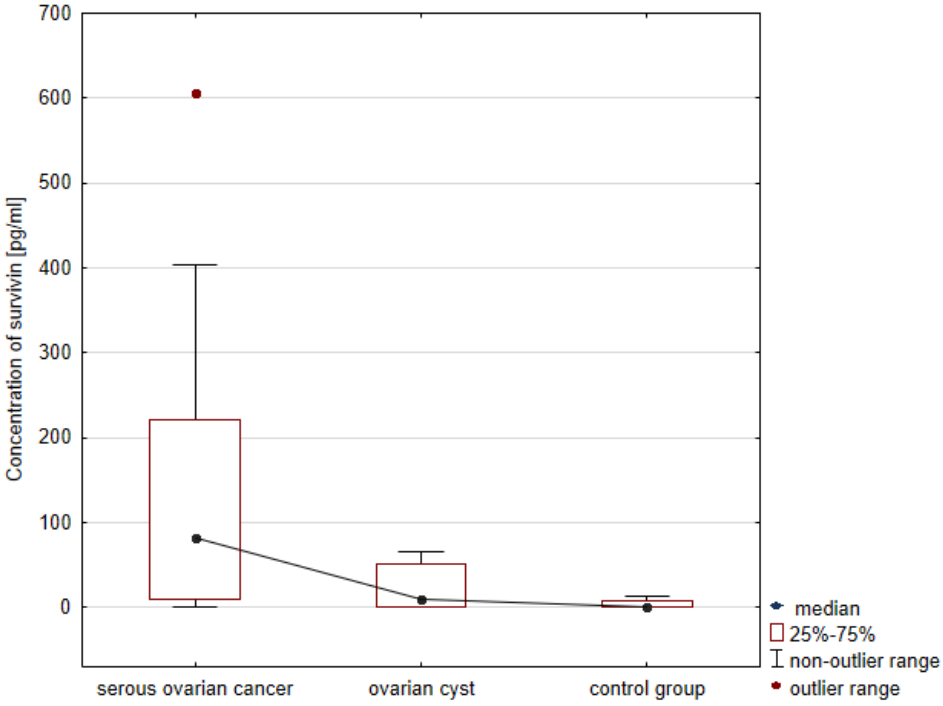

Figure 1. The concentration of survivin in the serum of the patients with serous ovarian cancer, an ovarian cyst and the control group

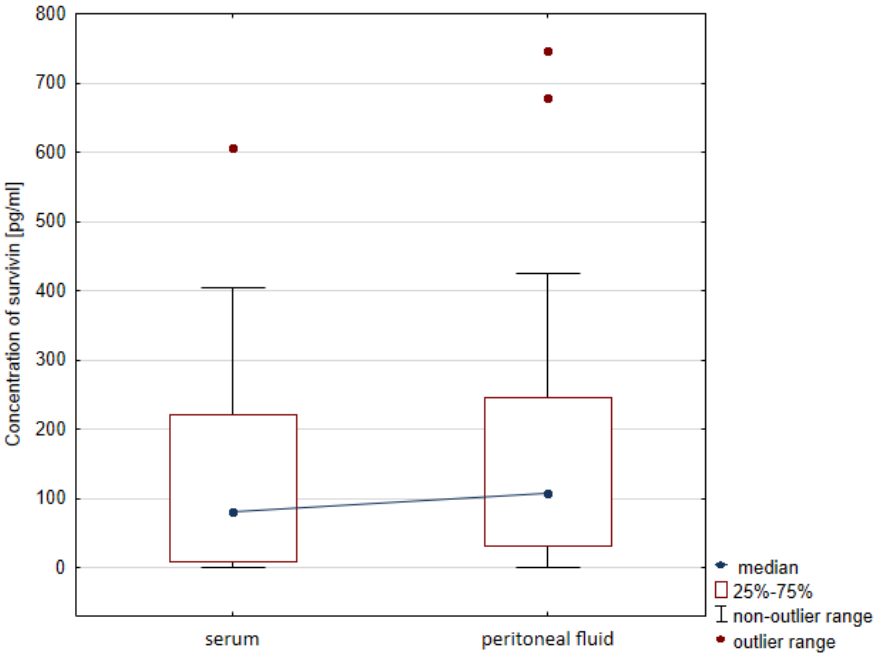

Figure 2. The concentration of survivin in the serum and peritoneal fluid of the patients with serous ovarian cancer

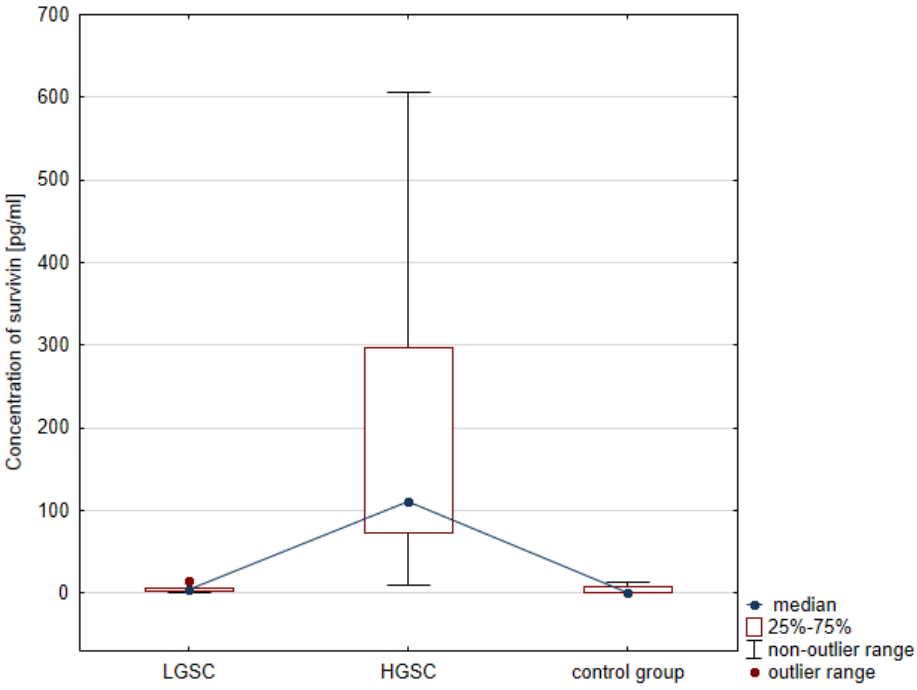

Figure 3. The concentration of survivin in the serum of the patients with ovarian cancer depending on the degree of cancer differentiation and the control group

HGSC — high-grade serous carcinoma; LGSC — low-grade serous carcinoma

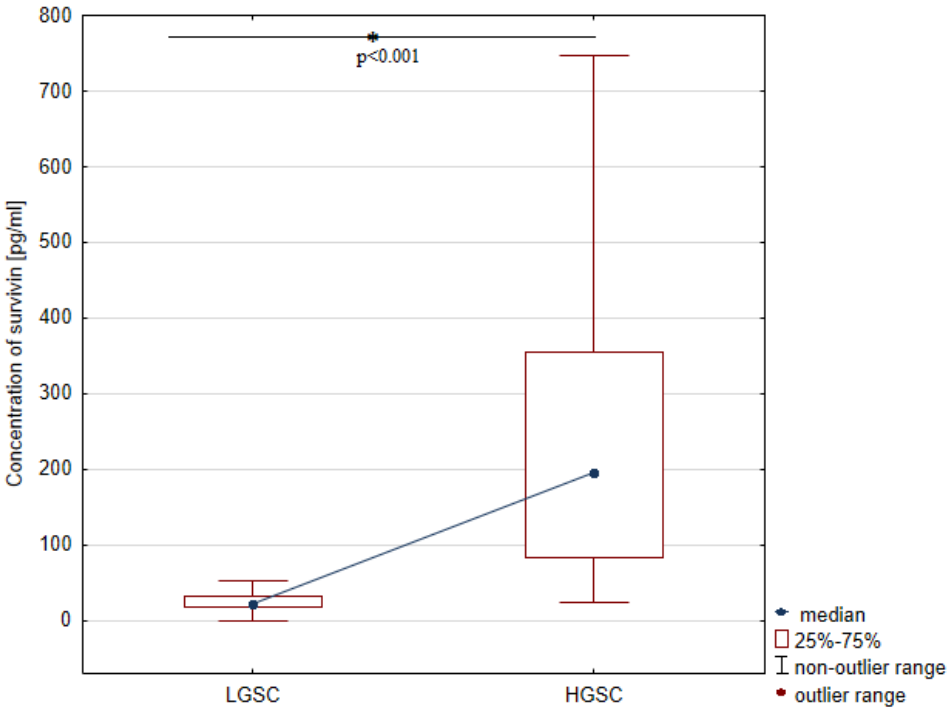

Figure 4. The concentration of survivin in the peritoneal fluid of the women with ovarian cancer depending on the degree of cancer differentiation

HGSC — high-grade serous carcinoma, LGSC — low-grade serous carcinoma

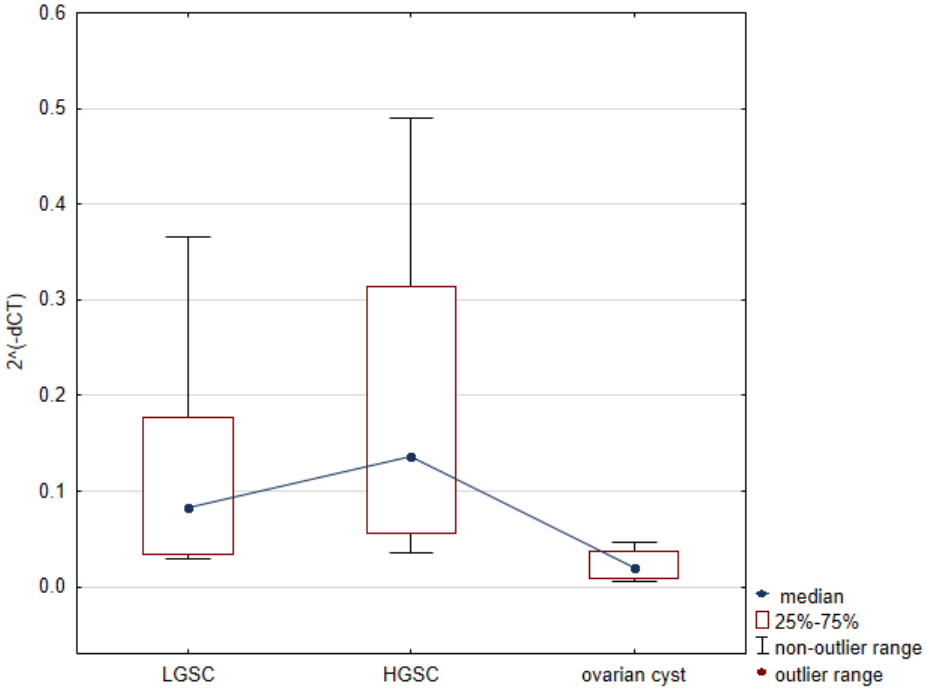

Figure 5. mRNA *BIRC5* expression in an ovarian cyst or cancer tumor depending on the degree of cancer differentiation

HGSC — high-grade serous carcinoma); LGSC — low-grade serous carcinoma