

Novel clinical and morphological predictors of malignancy in patients with ovarian endometrioid cysts

L.M. Mikhaleva¹, O.I. Patsap², T.V. Bezuglova¹, A.I. Davydov³, [G.M. Aliev](#)^{1,3,4}

¹ Research Institute of Human Morphology, Moscow, Russia

² Federal Center of Brain Research and Neurotechnologies of the Federal Medical Biological Agency, Moscow, Russia

³ I.M. Sechenov First Moscow State Medical University (Sechenov University), N.V. Sklifosovsky Institute of Clinical Medicine, Moscow, Russia

⁴ GALLY International Research Institute, San Antonio, TX, USA

Introduction. Endometriosis is an endless source of scientific investigations, but still the mechanisms of malignant transformation of ovarian endometriosis remain to be understood.

Patients and methods. This study was conducted on surgical specimens isolated from ovarian endometrioid cysts (OEC) and the endometriosis-associated ovarian tumors obtained after surgical operation from 117 patients. The normal level of serum CA 125 was assumed to be up to 35 IU/ml. Immunohistochemical study of MCK, CK7, CK20, CK 8/18, Calretinin, EMA, Ki67, CEA, Vimentin, Inhibin, WT1, p53, ARID1A (BAF250a), CA 125 antibodies was performed.

Results. The results revealed a direct correlation between the level of serum CA 125 and the WT1 expression in the OEC epithelium (Pearson $r=0.84$, $p<0.0001$) and between the level of serum CA 125 and the p53 expression (Pearson $r=0.81$, $p<0.0001$). A striking direct correlation was found when studying the relationship between WT1 and p53 expression in OEC epithelium (Pearson $r=0.79$, $p<0.0001$).

Conclusion. This research delineated the changes in OEC epithelium, which were similar to the serous epithelial type and associated with an extensive rise in the serum biomarker CA 125 level, which could be indicative of the early neoplastic transformation of OEC.

Keywords: CA 125, WT1, p53, ovarian endometrial cyst, ARID1A, malignant transformation

Corresponding author: Olga I. Patsap. E-mail: patsap.o@fccps.ru

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Новые клинко-морфологические предикторы неопластической трансформации у пациенток с эндометриодными кистами яичников

Л.М. Михалева¹, О.И. Пацап², Т.В. Безуглова¹, А.И. Давыдов³, [Г.М. Алиев](#)^{1,3,4}

¹ ФГБНУ Научно-исследовательский институт морфологии человека, Москва, Россия

² ФГБУ Федеральный центр мозга и нейротехнологий ФМБА России, Москва, Россия

³ Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский университет), Институт клинической медицины имени Н.В. Склифосовского, Москва, Россия

⁴ Международный научно-исследовательский институт GALLY, Сан-Антонио, Техас, США

Введение. Проблема эндометриоза является неиссякаемым источником для научных исследований, при этом механизмы злокачественной трансформации эндометриоза яичников все еще остаются недостаточно изученными.

Материалы и методы. Исследование проведено на операционном материале эндометриодных кист яичников (ЭКЯ) и опухолей яичников, полученных после хирургических операций у 117 пациенток. Нормальным уровнем сывороточного онкомаркера СА 125 были приняты значения до 35 МЕ/мл включительно. Иммуногистохимическое исследование проводилось с использованием маркеров МСК, СК7, СК20, СК 8/18, Calretinin, EMA, Ki67, CEA, Vimentin, Inhibin, WT1, p53, ARID1A (BAF250a), СА 125.

Результаты. Выявлена прямая корреляция между уровнем сывороточного СА 125 и экспрессией WT1 в эпителии ЭКЯ (коэффициент Пирсона, $r=0,84$, $p<0,0001$) и между уровнем сывороточного СА 125

и экспрессией p53 в эпителии ЭКЯ ($r=0,81$, $p<0,0001$). Сильная прямая корреляция обнаружена при изучении взаимосвязи между экспрессией WT1 и p53 в эпителии ЭКЯ ($r=0,79$, $p<0,0001$).

Заключение. По результатам данного исследования выявлены изменения в эпителии ЭКЯ с иммунофенотипом, подобным серозному эпителию, и эти изменения связаны со значительным повышением уровня сывороточного биомаркера СА 125, что может указывать на раннюю неопластическую трансформацию ЭКЯ.

Ключевые слова: СА 125, WT1, p53, эндометриоидная киста яичника, ARID1A, злокачественная трансформация

Для корреспонденции: Ольга Игоревна Пацап. E-mail: patsap.o@fccps.ru

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Introduction

Endometriosis takes the third place in all gynecological diseases after inflammation and leiomyoma. The incidence of endometriosis in fertile women ranges up to 15% and is one of the most common causes of infertility and chronic pelvic pain syndrome [1–4].

Endometriosis is characterized by ectopic tissue morphologically similar to the endometrium, with glands and stroma. To date, many theories have been proposed, which highlight the etiology, pathogenesis, and natural history of the endometriosis and endometriosis-associated tumors with genetic alterations, changes in the microenvironment, stress factors, etc., but none of them can explain the entire variety of its forms and ability to neoplastic transformation [1, 2, 5–7].

The history of malignant transformation of endometriosis started in 1925 when John Sampson first described endometriosis-associated malignancy criteria [8]. Malignant transformation of endometriosis is a rare phenomenon that occurs in about 0.7–2.5% of cases and, when it occurs, it usually involves the ovary [1, 9, 10]. Endometriotic foci also were identified near ovarian epithelial carcinomas and within these carcinomas. So, they were named endometriosis-associated tumors and included predominantly endometrioid, clear-cell carcinomas, and a minor group of seromucinous tumors [11, 12]. The risk of endometrioid and clear-cell ovarian tumors is 2–3 times higher in women with endometriosis [10, 13]. Further investigation led to discovering so-called “atypical” endometriosis. It consumes gradual changing of normal endometrioid cyst epithelium into atypical endometriosis with loss of nuclear polarity, hyperchromic nuclei, syncytial papillary changes, large hobnail cells, and then into invasive carcinoma [10]. Endometriosis was significantly associated with borderline ovarian tumors and endometriosis-associated ovarian carcinomas [14]. Atypical endometriosis and endometriosis-associated ovarian tumors have similar molecular changes, such as *PTEN*, *ARID1A*, and *HNF-1b* mutations. Moreover, *ARID1A* mutations were observed in clear-cell tumors

and atypical endometriosis but not in distant endometrioid foci [10, 15].

The mechanisms of malignant transformation of endometriosis such as genetic, epigenetic factors, microenvironment have been reported earlier [1–15]. The following neoplastic transformation pathways make a significant contribution to the development of “atypical” endometriosis and endometriosis-associated tumors. These include *KRAS/BRAF* mutations, *TP53* mutations, mTOR pathway, *ARID1A* mutation, iron metabolism, redox molecules in endometriotic cyst fluid, etc. Previous investigation has revealed a number of pathophysiological changes in endometriosis-associated carcinomas, such as deregulated oxidoreductase activity, metabolism, hormone activity, inflammatory response, innate immune response, and cell-to-cell signaling [16]. DNA methylation and demethylation, histone modifications, and miRNA aberrant expressions play a significant role in endometrioid ovarian cyst (OEC) malignant transformation [17]. PI3K-AKT-mTOR, chromatin remodeling (*ARID1A*), Notch signaling, and Wnt/ β -catenin pathway may contribute to OEC malignant transformation [1, 18–20].

Apart from the OEC malignant transformation, such cases have been reported from extraovarian endometriosis, including vaginal, ureteral, or cesarian scar. Most of the extraovarian malignancies are clear-cell or endometrioid carcinomas [21–26]. However, there are rare cases where rhabdomyosarcoma arises from OEC [27].

As previously mentioned, endometriosis-associated tumors could arise from endometrioid cysts [28]. There are reports available that cystic fluid contains several active biomolecules, such as iron, reactive oxygen species, interleukins. Iron-induced oxidative stress and DNA mutations are the basis of iron carcinogenesis, which are followed by the subsequent synthesis of the antioxidants with the decrease in cellular oxidative stress capacity, promotion of apoptosis resistance, and leading to tumor initiation and progression [29, 30]. So, with the help of metallobiology technology, these molecules can be used as non-invasive

biomarkers for detecting the endometriosis malignant transformation [31, 32].

World Health Organization approved the classification of ovarian tumors in 2014 that include high-grade and low-grade serous carcinomas (HGSC and LGSC, respectively) that differ from each other in genetic disorders, clinical course, and origin [33]. The source of HGSC is the fallopian tube epithelium implanted on the ovarian surface. It is associated with the fallopian tube's serous intraepithelial carcinoma (STIC) and *TP53* mutations [11]. LGSC is characterized by *KRAS* and *BRAF* mutations and develop sequentially from serous borderline tumors [11].

Glycosylation disorders are known as cancer markers. They lead to tumor-associated glycans and glycoproteins production. The glycosylation marker CA 125 is used for detecting and monitoring serous ovarian tumors. Since glycosylation changes are the early event in the tumor, the identification of tumor-associated markers of glycosylation is an effective strategy in early diagnosis and improving the treatment [34].

The level of serum CA 125 detected in 1% of healthy female donors can be 35 IU/ml and is often regarded as the upper limit of the normal reference in the clinical practice. It should be noted that this level is controversial, for example, in postmenopausal women or in patients after hysterectomy, the level of CA 125 tends to decrease, and the lower level may be more acceptable [35]. Approximately 85% of patients with ovarian epithelial tumors have a serum CA 125 level higher than 35 IU/ml. Serum CA 125 is less often increased in mucinous, clear-cell, and borderline tumors than in serous carcinomas. An increase in serum CA 125 level may also be associated with other malignancies (pancreas, breast, colon, lung tumors) and benign or physiological conditions, including pregnancy, endometriosis, and menstruation [35].

Regarding CA 125 as a marker of endometriosis, many authors are inclined to believe that the level of CA 125 ≥ 30 IU/ml is an indicator of endometriosis with high accuracy only in women with symptoms of pain and infertility. CA 125 should be considered a discriminatory test for suspected endometriosis, and the level of CA 125 < 30 IU/ml, however, cannot be a criterion for reliable detection of endometriosis [36–39].

The present work suggested that an increased level of serum CA 125 in patients with OEC indicates a change in the morphology and physiology of endometrioid epithelium, reflecting the beginning of the neoplastic transformation of OEC.

The efficient understanding of biological and functional mechanisms depicting OEC complex pathogenesis is considered a significant aspect for developing novel diagnostic and therapeutic strategies. Furthermore, the neoplastic transformation of ovarian endometriosis remains to be understood fully despite decades of research. The present study delineated an extensive rise in the serum levels of CA 125 in OEC conditions, which indicates a change in the morphology and physiology of endometri-

oid epithelium conducive to the possible beginning stage of neoplasm.

Patients and methods

The present study was conducted on the surgical specimen samples obtained from 117 patients. 104 patients were after cystectomy with endometrioid cysts and 13 with ovarian tumors, including endometriosis-associated ones. The age group was chosen from 20 to 83 years (average 36.58 ± 0.95 years) during the period of 2016 to 2019 admitted to the Hospital of S.S. Udina City of Moscow Hospital and the Moscow Clinical Hospital #31. All patients agreed and provided their individual informed consent to analyze their surgical specimen samples with complete Institutional ethical guidelines. Normal range of serum CA 125 was admitted under 35 IU/ml. We divided patients into five groups based on obtained data:

- group 1 includes OEC with normal levels of serum CA 125 cancer biomarker in 69 patients,
- group 2 includes an increased level of serum CA 125 (36–60 IU/ml) in 17 patients,
- group 3 includes an increased level of serum CA 125 (61–90 IU/ml) in 10 patients,
- group 4 includes an increased level of serum CA 125 (91–301 IU/ml) in 8 patients,
- and group 5 includes ovarian carcinomas, i.e., endometrioid (endometriosis-associated ones), serous low- and high-grade with solid, pseudo-endometrioid, transitional cell-like pattern (SET-type) in 13 patients. The serum CA 125 analysis was performed at various laboratories in Moscow using immunochemiluminescent analyzers Architect 1000i (USA) and Immulite 1000 (Japan).

Reagents

To compare expression in OEC with ovarian tumors, we used a diagnostic panel of mouse monoclonal antibodies against MCK, CK7, CK20, CK 8/18, Calretinin, EMA, Ki67, CEA, Vimentin, Inhibin, WT1, CA 125, ARID1A (BAF250a) (Santa Cruz, USA).

Immunohistochemistry

OEC and endometriosis-associated tumors surgical specimens were collected into buffered neutral 10% formalin and subjected to fixation. Paraffin-embedded tissue blocks were prepared through routine histological processing. Immunohistochemical analysis was executed with the aid of the avidin-biotin complex technique. Histological sections were made using Sakura rotary microtomes, stained with hematoxylin and eosin. Immunohistochemistry study of MCK, CK7, CK20, CK 8/18, Calretinin, EMA, Ki67, CEA, Vimentin, Inhibin, WT1, CA 125, ARID1A (BAF250a) antibodies was performed using “Leica Bond-maX” immunostainers (Germany).

Interpretation of the immunohistochemical results was carried out considering the localization of positive cells by counting both the number of colored epithelial cells

per 100 cells in 10 high power fields ($\times 400$ /HPF) and the intensity of staining. The obtained quantitative results were expressed as a percentage, where 0 – lack of expression, 1 – up to 50% of colored cells – focal expression, 2 – more than 50% of colored cells – intense expression of the marker.

The intensity of cytoplasmic expression of the marker was evaluated in points, where 0 – lack of expression, 1 – weak (pale) cell staining, 2 – moderate cell staining, 3 – intense (bright) cell staining.

Ki67 expression was evaluated as follows: 1) 0–20% – low proliferative activity, 2) 21–50% – moderate proliferative activity, 51–100% – high proliferative activity.

The expression of p53 in a weakly positive reaction was considered corresponding to the wild-type of *TP53* gene (weakly positive staining), with total negative or staining of more than 80% of the nuclei referred to mutant-type of *TP53* gene.

Statistics

Statistical analysis of results was performed using descriptive statistics and a paired t-test, and a correlation between the expression of immunohistochemical markers in OEC epithelial and stromal cells and the level of serum CA 125. The reliability of the differences in the mean values was calculated using the analysis of variance. The correlation analysis results estimated the relationship between the studied parameters with the Pearson correlation coefficient calculation (r). Also, the nonparametric Mann–Whitney criteria and the Spearman rank correlation coefficient were used in the calculation in cases where parametric statistics methods were incorrect. The data was presented as $M \pm m$, where M is the arithmetic mean and m is the mean's statistical error. A P-value of 0.05 was considered the cutoff for statistical significance.

Results

Most patients with OEC (groups 1–4) (98.1%) and with endometriosis-associated carcinomas (group 5) (82%) reported nagging pains in the lower abdomen with varying frequency during the menstrual cycle. The body mass index (BMI) ranged from 16.8 to 43 (average 23.08 ± 0.48) in OEC (groups 1–4) and from 18 to 28 (average, 23.77 ± 0.8) in group 5, the age of menarche was from 11 to 18 years (average 13.09 ± 0.13 years) in groups 1–4 and 11 to 16 (average, 12.77 ± 0.4) in group 5. The diameter of OEC ranged from 15 to 135 mm (average 61.54 ± 2.72 mm) in groups 1–4 and from 20 to 240 mm (average 93.8 ± 16.7 mm). Bilateral OEC were detected in 16 patients (13.68%) in groups 1–4. Gynecological diseases combined with OEC (groups 1–4) included cervical ectopy in 43 patients (41.3%), endometrial hyperplasia in 4 (3.8%), infertility I in 2 (1.9%), leiomyoma in 12 (11.5%), adenomyosis in 2 (1.9%), endometrial polyp in 12 (11.5%), endocervical polyp in 4 (3.8%), chronic salpingoophoritis in 5 (4.8%), and less than in 1% observed ovarian apoplexy, mature cystic teratoma, paraovarian cyst, cervical leukoplakia, HSIL,

and chronic endometritis. Three (3) patients had a history of breast fibroadenoma (2.9%). Twenty-five (25) (24%) patients had no combined gynecological pathology, and 20 (19%) patients had more than two diseases (Fig. 1). Gynecological diseases combined with endometriosis-associated tumors (group 5) included leiomyoma in 1 patient (7.7%).

Combined gynecological diseases in OEC patients

Expression of MCK, CK7, CK8/18, and EMA markers in OEC and endometriosis-associated ovarian tumors did not differ in all groups and were expressed in all cases. Expression of CK20, CEA, Calretinin, Inhibin, and Vimentin in OEC epithelium and endometriosis-associated ovarian tumors was negative. The expression of proliferation marker Ki67 in OEC did not exceed 5% in all cases. In contrast, its expression in ovarian tumors was 10–15% in endometrioid and low-grade serous carcinomas and 50–71% in high-grade serous carcinoma (SET-type). Expression of the immunohistochemical marker CA 125 was higher in serous ovarian tumors and in the OEC group with elevated serum CA 125 levels above 60 IU/ml. *ARID1A* (BAF250a) expression was 70–96% (average $83.73 \pm 0.67\%$) in all groups of OEC, 10–43% (average $21.6 \pm 4.5\%$) in endometrioid ovarian carcinomas and 60–67% (average $64 \pm 1.4\%$) in serous carcinomas low- and high-grade (Table 1).

Significant changes in nuclear expression were detected when evaluating the immunohistochemical reaction for WT1 and p53 expression. The WT1 gene located on chromosome 11p13 provides protein synthesis is required for the development of normal kidneys and gonads. WT1 protein is a transcription factor significantly involved in the growth, maturation, cell differentiation, and apoptosis in these tissues. The characteristic feature for serous differentiation of OEC epithelial cells is an intense nuclear expression of WT1 both in individual cells and in a group of epithelial cells.

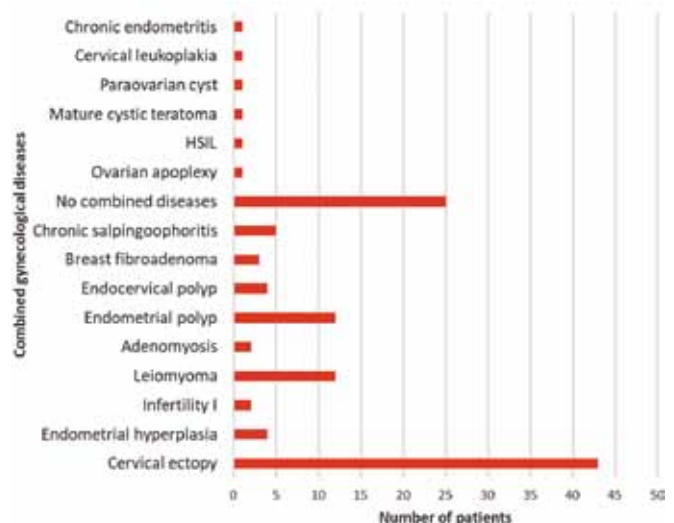


Fig. 1. Combined gynecological diseases in OEC patients

Рис. 1. Комбинированные гинекологические заболевания у пациенток с ЭКЯ

Table 1 | Таблица 1

Expression of IHC markers in all groups |
Экспрессия ИГХ маркеров во всех группах

Group Группа	MCK	CK7	CK8/18	EMA	Ki-67	WT1	p53	CA125	ARID1A BAF250
1 (0–35 UE/ml) МЕ/мл)	3+	3+	3+	3+	1–2%	0–2% (0.17±0.1%)	Wild-type Дикий тип, 0–15% (2.6±0.5%)	1–2+	3+
2 36–60 UE/ml) МЕ/мл)	3+	3+	3+	3+	1–2%	0–6,5% (0.76±0.37%)	Wild-type Дикий тип, 1–54% (18.74±3.52%)	1–2+	3+
3 (61–90 UE/ml) МЕ/мл)	3+	3+	3+	3+	2–3%	0–58% (20.7±6.4%)	Wild-type Дикий тип, 3–60% (31.7±7.6%)	2–3+	3+
4 (91–301 UE/ml) МЕ/мл)	3+	3+	3+	3+	2–4%	62–86% (77±3.01%)	Mutant-type Мутантный тип, 14–93% (71.9±8.9%)	2–3+	3+
5 endometrioid эндометриоидные	3+	3+	3+	3+	10–15%	0%	Wild-type Дикий тип	1–2+	Loss of expression in 60% of cells Потеря экспрессии в 60% клеток
5 serous low-grade low-grade серозные	3+	3+	3+	3+	10–15%	35–50%	Wild-type Дикий тип	2–3+	3+
5 serous high grade (SET-type) high-grade серозные (SET-типа*)	3+	3+	3+	3+	50–71%	50–80%	Mutant-type Мутантный тип	2–3+	3+

*SET-тип – серозная карцинома high-grade с солидными, эндометриоидными и переходноклеточными участками строения.

The nuclear expression of WT1 in the OEC epithelium was predominantly negative in the patients of 1–2 group with serum CA 125 levels up to 60 IU/ml (0–35; 36–60 IU/ml). However, a few positive nuclear expression cases of WT1 were observed in individual epithelial cells and were up to 6.5% (average 0.4±0.1%). Positive nuclear expression was observed in stromal cells in all cases in all groups and was 41–78.3% (average 67.9±5.6%). Patients with elevated levels of serum CA 125 61–90 IU/ml showed a positive nuclear expression up to 58% (average 20.7±6.4%) of OEC epithelial cells. Patients with elevated levels of serum CA 125 91–301 IU/ml demonstrated the positive nuclear expression in 62–86% epithelial cells (average, 77.0±3.01%). Positive nuclear expression of WT1 was also observed in stromal cells in all cases in 47–56% (average, 51.6±5.2%) of cells (Fig. 2, 3).

Correlation between the serum CA 125
and WT1 expression in epithelial and stromal OEC
clinicopathology

Relationship between levels of serum CA 125 and WT1,
p53, ARID1A (BAF250a) expression in epithelial and
stromal OEC clinicopathology

WT1 nuclear expression was observed focally in OEC epithelium along with epithelium with a negative reaction. It was noted that with an increase in serum CA 125 level, there was an increase in the number of such foci. However,

even at level 301 IU/ml, foci of epithelium with a negative expression remained in OEC. The expression of WT1 was ambiguous in 13 patients with ovarian carcinomas: group of endometrioid carcinomas (n=9): 8 exhibited negative expression, 1-weak focal and uneven (about 1% of cells); group of serous tumors (low-grade, n=3) was 35–50% and in serous carcinoma high-grade (SET-type), n=1, it was 50–80%.

The expression of protein p53 was predominantly wild-type, while the percentage of nuclear expression in

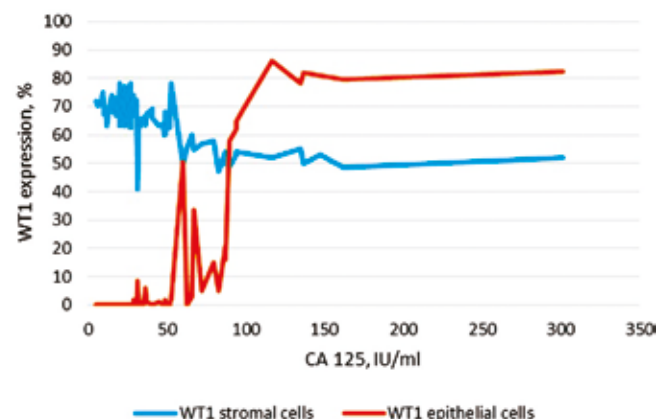


Fig. 2. WT1 expression in OEC epithelial and stromal cells
Рис. 2. Экспрессия WT1 в эпителиальных и стромальных
клетках ЭКЯ

Serum CA 125 level,
IU/ml |
Уровень сывороточного
СА 125, МЕ/мл

Under 60 IU/ml |
Менее 60 МЕ/мл

More than 60 IU/ml
in negative WT1
expression areas |
Свыше 60 МЕ/мл
в областях с негативной
экспрессией WT1

More than 60 IU/ml
in positive WT1
expression areas |
Свыше 60 МЕ/мл
в областях
с положительной
экспрессией WT1

WT1 expression |
Экспрессия WT1

p53 expression |
Экспрессия p53

ARID1A (BAF250a)
expression |
Экспрессия ARID1A
(BAF250a)

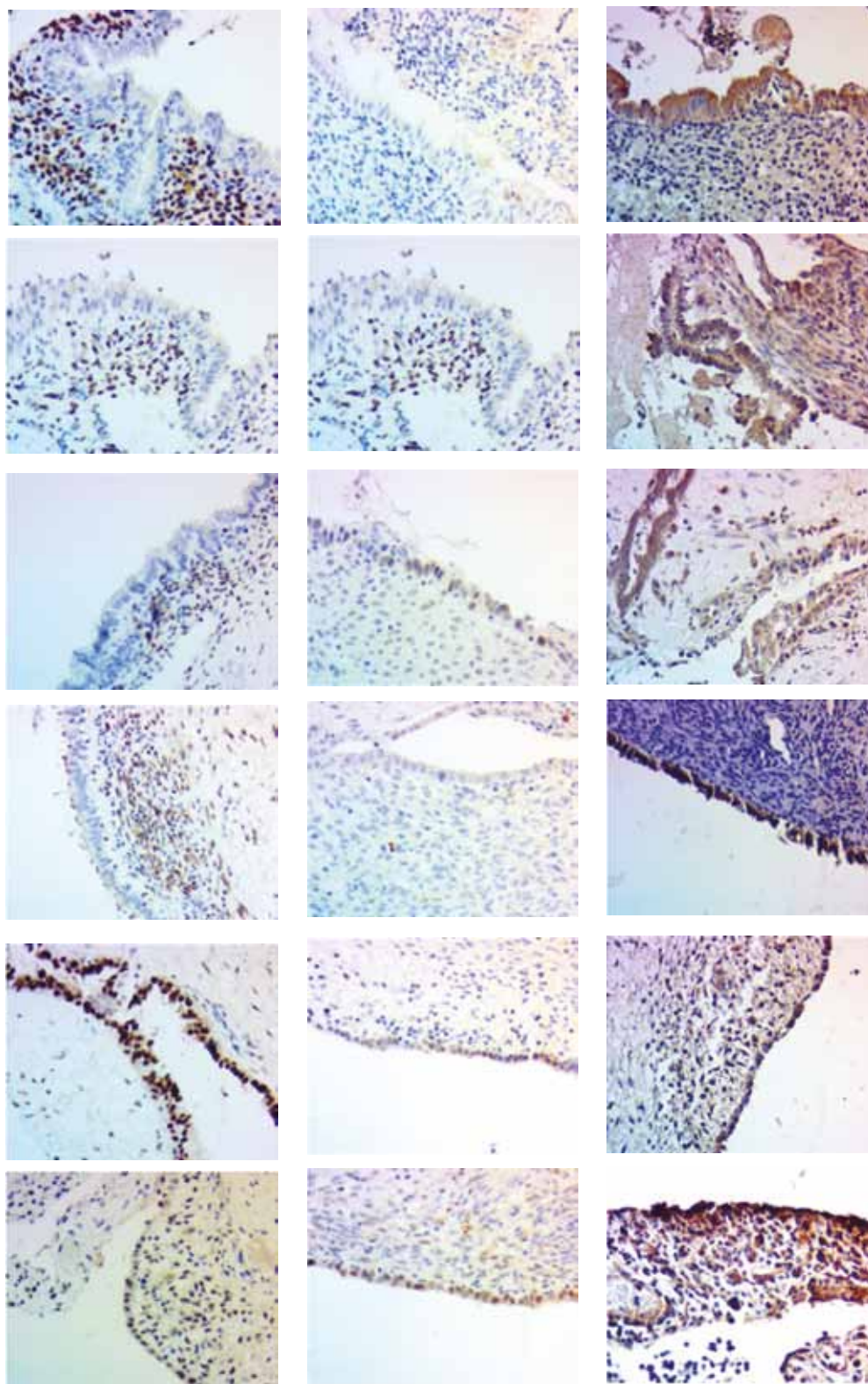


Fig. 3. WT1, p53, and ARID1A (BAF250a) expression in OEC epithelial and stromal cells

Рис. 3. Экспрессия WT1, p53 и ARID1A (BAF250a) в эпителиальных и стромальных клетках ЭКЯ

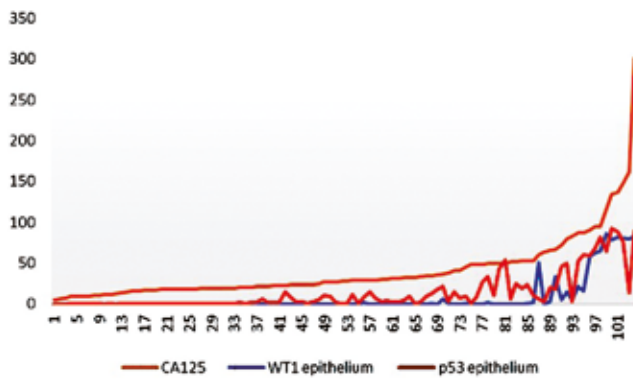


Fig. 4. WT1 and p53 expression in OEC epithelial cells

Рис. 4. Экспрессия WT1 и p53 в эпителиальных клетках ЭКЯ

OEC epithelial cells gradually but unevenly increased with increasing level of serum CA 125 and ranged from 0 to 75% (average $13.77 \pm 2.21\%$) in 99 cases. The expression level of p53 was over 80% in 4 cases with serum CA 125 levels 94.3–301 IU/ml, which is an indicator of pathological expression of p53 (Fig. 3, 4). P53 expression was predominantly wild-type, and the percentage of expression was 15–82% (average $33.56 \pm 4.6\%$) in endometrioid and serous low-grade ovarian tumors, and the mutant-type expression was detected in high-grade serous carcinoma (SET-type).

WT1 and p53 expression in OEC epithelial cells

Statistical analysis of this data was completed. We have identified a strong direct correlation between the serum CA 125 level and the WT1 expression level in the OEC epithelium (Pearson correlation coefficient (r) = 0.84, $p < 0.0001$) and between the serum CA 125 level and p53 expression

(Pearson, $r = 0.81$, $p < 0.0001$). There was a moderate inverse relationship between the serum CA 125 level and the WT1 expression level in the OEC stroma (Pearson, $r = -0.68$, $p = 0.002$) and between WT1 expression in the epithelium and stroma of OEC (Pearson, $r = -0.69$, $p = 0.5$).

When studying the relationship between the expression of WT1 and p53 in the OEC epithelium, a strong direct correlation was revealed (Pearson, $r = 0.79$, $p < 0.0001$), which may be associated with early neoplastic transformation.

BMI and OEC diameter were also evaluated in this study [40, 41]. Studies of the Pearson correlation coefficient for samples over 60 were conducted, and nonparametric statistics such as the Mann–Whitney coefficient (U) and Spearman correlation coefficient (P) were evaluated. When evaluating the Mann-Whitney coefficient, no differences were found in the samples in groups I–II and V. Significant differences in the samples were found in groups III and IV. At the same time, there was no significant correlation between the size of the OEC, BMI, and the expression of CA125, WT1, and p53 in groups I–II (0–60 IU/ml), the Spearman coefficient ranges -0.02 – 0.4 , which indicates a weak direct/inverse correlation. In group III (61–90 IU/ml), a moderate direct relationship was found between the OEC size and the expression of the immunohistochemical markers WT1 and p53 and a moderate inverse relationship between BMI and the level of p53 expression. There was a moderate direct relationship between the OEC size and the level of serum CA 125, as well as the level of p53 expression, and a moderate inverse relationship between BMI and WT1 expression in group IV (91–301 IU/ml). A moderate inverse relationship between BMI and WT1 expression was also found in the group of ovarian tumors. Summary data of parametric and nonparametric correlation in OEC groups are in Table 2a, 2b.

Table 2a | Таблица 2а

Summary data of correlation in all OEC groups (Pearson, r) |
Сводные корреляционные данные во всех группах ЭКЯ (критерий Пирсона, r)

	Serum CA 125, IU/ml Уровень СА 125 в сыворотке крови, МЕ/мл	Body mass index, kg/m ² Индекс массы тела, кг/м ²	OEC diameter, mm Диаметр ЭКЯ, мм	P53 expression in epithelium, % Экспрессия P53 в эпителии, %	WT1 expression in epithelium, % Экспрессия WT1 в эпителии, %
Serum CA 125, IU/ml Уровень СА 125 в сыворотке крови, IU/ml	–	–0,14	0,09	0,81	0,84
Body mass index, kg/m ² Индекс массы тела, кг/м ²	–0,14	–	–0,06	–0,14	–0,11
OEC diameter, mm Диаметр ЭКЯ, мм	0,09	–0,06	–	0,14	0,11
P53 expression in epithelium, % Экспрессия P53 в эпителии, %	0,81	–0,14	0,14	–	0,79
WT1 expression in epithelium, % Экспрессия WT1 в эпителии, %	0,84	–0,11	0,11	0,79	–

**Correlation between BMI/OEC diameter and WT1, p53 expression depending on serum CA 125 level (Spearman, rs) |
Корреляция между индексом массы тела (ИМТ)/ и диаметром ЭКЯ и экспрессией маркеров WT1, p53
в зависимости от сывороточного уровня СА 125 (IU/ml | МЕ/мл) (критерий Спирмана, rs)**

Groups Группы	OEC diameter Диаметр ЭКЯ			BMI ИМТ		
	WT1	p53	CA 125	WT1	p53	CA 125
I (CA 125 = 0–35 IU/ml МЕ/мл)	–0,2	0,2	0,09	–0,1	–0,16	–0,14
II (CA 125 = 36–60 IU/ml МЕ/мл)	0,4	0,01	–0,02	–0,2	–0,22	–0,2
III (CA 125 = 61–91 IU/ml МЕ/мл)	0,5	0,6	0,3	–0,35	–0,6	–0,3
IV (CA 125 = 90–301 IU/ml МЕ/мл)	0,24	0,57	0,65	–0,57	–0,19	–0,4
V (ovarian tumors опухоли яичника)	–0,1	–0,2	–0,3	–0,6	–0,1	–0,3

Discussion

CA125 is a significant marker, and it is mostly used to identify disease conditions, including OEC. Predominantly, the CA125 levels are reported to be enhanced in 80–85% in females with advanced stages of ovarian cancer and endometriosis. Hence, it is referred to as a suitable cancer marker to monitor ovarian tumor progression, differentiation, and regression to foster early diagnosis [38]. A plethora of research studies established a positive link between endometriosis and certain groups of ovarian tumors, such as endometrioid, clear-cell, and serous low-grade, based on data from more than 21,000 patients [42]. Yiyang Wang et al. reported that the immunohistochemical expression of markers OVGPI, WT1, and FMO in LGSCs and concluded these carcinomas develop from tubal-type epithelium of ovarian cystic inclusions [43, 44]. Abnormal expression of the WT1 protein is well known as a serous differentiation marker since it has a positive expression in serous ovarian tumors [45, 46]. A method exists for differential diagnosis of ovarian HGSC and LGSC based on the p53/P16 ratio. However, the authors of this study noted that routine morphological diagnosis is better associated with the patient survival outcome [47]. The same authors provide data that WT1 expression was observed in 71.4% of LGSC and 57.1% of HGSC, p53 expression was completely negative in 81% of LGSC and 30.6% of HGSC, focal in 9.5% of LGSC and 1.2% of HGSC, diffuse in 9.5% of LGSC and 68.2% of HGSC [47]. Other investigators did not find p53 expression in solitary endometriosis, and endometriosis coexisted with endometriosis-associated tumors [48]. However, they explored a small sample of 29 cases without any significant correlations with serum biomarkers. Ma X et al. suggested that PTEN mutation is an early indicator and p53 mutation is a later indicator in malignant transformation of endometriosis [49]. We also found p53 expression over 75% in 5 cases with serum CA 125 levels 94.3–301 IU/ml, which may reflect the serous epithelial transformation that had existed for a long time and possibly is at the beginning of neoplastic changes.

According to our data, there was focal serous differentiation of OEC epithelium with expression of serous markers such as WT1 and p53 with an increase in the CA 125 level more than 60 IU/ml. We found that the IHC-profile for normal endometrioid epithelium was WT1-/p53wt/ARID1A+ and was characteristic for groups 1–2 (0–35; 36–60 IU/ml). When comparing the IHC-profile of OEC group 3 (61–90 IU/ml) with group 5 (endometriosis-associated tumors), we stated their equality, i.e., WT1+/p53wt/ARID1A+. Moreover, when we compare the IHC-profile of group 4 (91–301 IU/ml) to group 5, these were similar: WT1+/p53mt/ARID1A+. These findings suggest the neoplastic transformation to serous ovarian borderline tumors and LGSC. We found OECs share similar immunohistochemical profiles with serous ovarian carcinomas, but not with the endometrioid ones because the expression of WT1 and p53 were not observed, and there was no lack of ARID1A expression. The expressions of WT1 and p53 levels were focal across the endometrioid carcinomas. Besides, ARID1A (BAF250a) expression in OEC was close to that in serous low-grade carcinomas and differed from endometrioid ones. Moreover, there is a clinical case that demonstrated OEC malignant transformation to well-differentiated endometrioid carcinoma with normal serum CA 125 [50], which supports our supposition that OEC may transform to serous ovarian tumor, and this process is accompanied by an increase in serum CA 125 level.

Bulun et al. established that endometriotic stromal cells are mutation-free. We likewise found that the stromal cells did not display any changes in immunohistochemical marker expression. These authors have depicted that the stroma cells contain widespread epigenetic defects, which could alter gene expression and induce a progesterone-resistance and inflammation. Subsequent estrogenic action in the stroma results in paracrine signaling to neighboring epithelial cells, which may enhance proliferation, causing mutation accumulation and malignant transformation in OEC epithelial cells that may lead to epithelial ovarian cancer [51].

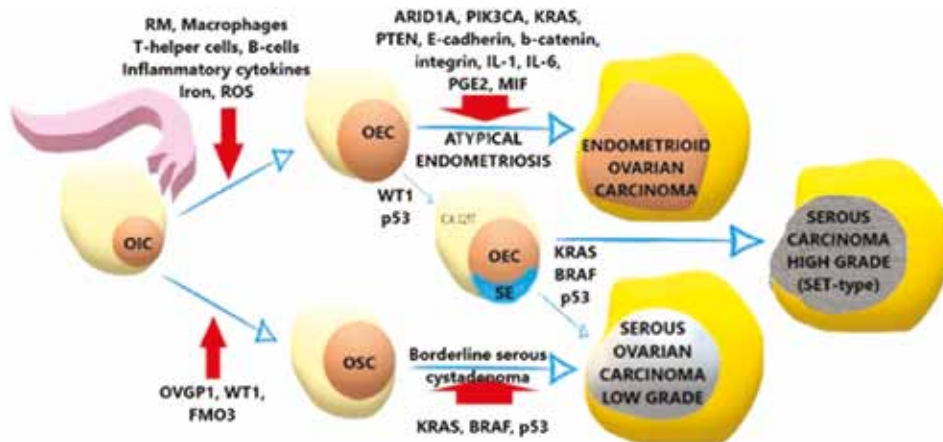


Fig. 5. Possible mechanisms of neoplastic transformations of OEC. OIC – ovarian inclusion cyst; OEC – ovarian endometrioid cyst; OSC – ovarian serous cystadenoma; RM – retrograde menstruation; ROS – reactive oxygen species; SE – serous epithelium; OVGP1 – oviduct-specific glycoprotein 1; WT1 – Wilm’s tumor protein; FMO3 – flavin-containing monooxygenase 3; *ARID1A* – AT-rich interactive domain-containing protein 1A; PIK3CA – phosphatidylinositol-3-kinase, catalytic subunit; KRAS – RAS/MAPK pathway protein; BRAF – v-RAF murine sarcoma viral oncogene homolog b; *PTEN* – homolog of phosphatase and tensin; IL-1 – interleukin 1; IL-6 – interleukin 6; PGE2 – prostaglandin E2; MIF – macrophage migration inhibitory factor; p53 – p53 protein; CA 125 – cancer antigen 125

Рис. 5. Предположительные механизмы неопластической трансформации ЭКЯ. OIC – инклюзионная киста яичника; OEC – эндометриоидная киста яичника; OSC – серозная цистаденома яичника; RM – ретроградная менструация; ROS – активные формы кислорода; SE – серозный эпителий; OVGP1 – яйцеводспецифичный гликопротеин 1; WT1 – белок опухоли Вильмса; FMO3 – флавиносодержащая монооксигеназа 3; *ARID1A* – AT-насыщенный интерактивный домен, содержащий белок 1A; PIK3CA – фосфатидилинозитол-3-киназа, каталитическая субъединица альфа; KRAS – белок пути RAS/MAPK; BRAF – гомолог b вирусного онкогена мышинной саркомы v-RAF; *PTEN* – гомолог фосфатазы и тензина; ИЛ-1 – интерлейкин 1; ИЛ-6 – интерлейкин 6; PGE2 – простагландин E2; MIF – фактор ингибирования миграции макрофагов; p53 – белок p53; CA 125 – опухолевый антиген 125

In this regard, a scheme for the possible development of ovarian carcinomas from OEC was proposed (Fig. 5). Our results reported that OEC could be precursors to both endometrioid carcinomas via the *ARID1A*, *PI3K/AKT*, *MAPK/ERK* pathways, and serous carcinomas via the *TP53*, *RAS/MAPK* pathways.

Conclusion

Evaluation of immunohistochemical expression of WT1 and p53 markers in the OEC with increased serum CA 125 level is beneficial to oncologists to choose a suitable therapeutic modality with adequate follow-up to the patients. Our present study results replicate previously published reports. Furthermore, the results indicate an early change in the epithelium that may give rise to neoplastic transformation is feasible. However, the mechanism of neoplastic transformation remains only partially understood and requires extensive research.

Human and animal rights

All the study procedures were approved by the US NIH Ethical Standards. Animals were not used for this study. Consent was obtained from all the humans in this study. The procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the NIH ethical guidelines.

Compliance with ethics guidelines

This article is based on research that was ethically approved by the Local Ethical Committee of the City Clinical Hospital No. 31, Moscow, and Institute of Human Morphology, Moscow, Russia (Approval Protocol No. 3, 12.06.2019).

Author contributions

Compiling and combining edits for additional drafts; assembly of data, results, and references; writing – original draft – L.M. Mikhaleva, O.I. Patsap.

Assembly of cases; slide scanning; survey creation, blinded review of slides – T.V. Bezuglova, A.I. Davydov, [G.M. Aliev](#).

Study conceptualization; digital slide review, writing – review, and editing – L.M. Mikhaleva, O.I. Patsap, [G.M. Aliev](#).

Each author has participated sufficiently in work to take public responsibility for the content as per ICMJE guidelines; authorship credit should be based on substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

Вклад авторов

Сбор данных, анализ результатов; написание оригинального текста статьи, составление списка литературы, внесение правок – Л.М. Михалева, О.И. Пацап.

Сбор клинических случаев; сканирование микропрепаратов; создание отчета об обследовании, анализ микропрепаратов слепым методом – Т.В. Безуглова, А.И. Давыдов, [Г.М. Алиев](#).

Концепция исследования; анализ оцифрованных микропрепаратов, написание обзора и редактирование текста – Л.М. Михалева, О.И. Пацап, Г.М. Алиев.

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Давыдов А.И., Михалева Л.М., Пацап О.И. К вопросу о маркерах ранней детекции эндометриоз-ассоциированных опухолей яичника. *Вопросы гинекологии, акушерства и перинатологии.* 2019;18(4):133–137. DOI: 10.20953/1726-1678-2019-4-133-137.
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Author information

Liudmila M. Mikhaleva – Dr. Sci. (Med.), Professor, Director, Head of the Laboratory of Clinical Morphology, Research Institute of Human Morphology.

<https://orcid.org/0000-0003-2052-914X>

Tatiana V. Bezuglova – Cand. Sci. (Biol), Deputy Director for Scientific Work, Research Institute of Human Morphology.

<https://orcid.org/0000-0001-7792-1594>

Olga I. Patsap – Head of the Department of Pathology, Federal Center of Brain Research and Neurotechnologies.

<https://orcid.org/0000-0003-4620-3922>

Aleksandr I. Davydov – Dr. Sci. (Med.), Professor, Professor of the Department of Obstetrics, Gynecology and Perinatology, N.V. Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University).

<https://orcid.org/0000-0001-5592-8429>

[Gjumrakch M. Aliev](#) – Cand. Sci. (Med.), President of the GALLY International Research Institute.

<https://orcid.org/0000-0001-7373-3182>

Информация об авторах

Людмила Михайловна Михалева – доктор медицинских наук, профессор, директор, заведующая лабораторией клинической морфологии НИИ морфологии человека.

Татьяна Васильевна Безуглова – кандидат биологических наук, заместитель директора по научной работе НИИ морфологии человека.

Ольга Игоревна Пацап – заведующая патологоанатомическим отделением Федерального центра мозга и нейротехнологий.

Александр Ильгизирович Давыдов – доктор медицинских наук, профессор, профессор кафедры акушерства, гинекологии и перинатологии Института клинической медицины им. Н.В. Склифосовского Первого МГМУ им. И.М. Сеченова (Сеченовский Университет).

[Гюмрах Магомедович Алиев](#) – кандидат медицинских наук, президент Международного научно-исследовательского института GALLY.