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EXPRESSION OF p53, p21$^{WAF1/CIP1}$, p16^{INK4A} AND Ki-67 PROTEINS IN SEROUS OVARIAN TUMORS

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***Aim*: The analysis of p53, p21$^{WAF1/CIP1}$, p16^{INK4a} and Ki-67 expression in serous ovarian carcinomas of different grade. *Materials and Methods:* In total, 43 ovarian adenocarcinomas and 8 non-altered ovarian epithelial tissues were immunohistochemically investigated for expression of Ki-67, p53, p21$^{WAF1/CIP1}$ and p16^{INK4a}. *Results:* It has been shown that expression of Ki-67, p53, p21$^{WAF1/CIP1}$ and p16^{INK4a} in non-altered ovarian epithelial tissue is absent. Serous ovarian carcinomas are characterized by high proliferative activity (PI Ki-67 = 30.0 ± 0.3%), p53 and p16^{INK4a} overexpression (LI is 40.3 ± 0.3% and 31.1 ± 0.6% respectively) and low expression of p21$^{WAF1/CIP1}$ (LI = 6.8 ± 0.3%). The association between expression of these markers and ovarian tumor grade was defined: the maximal level of Ki-67, p53 and p16^{INK4a} and minimal of p21$^{WAF1/CIP1}$ expression were observed in G3 tumors. So, low p21$^{WAF1/CIP1}$ expression (LI < 7.0%) combined with p16^{INK4a} overexpression is considered to be the factor for a poor prognosis in serous ovarian cancer. *Conclusions:* The present study has indicated that biomolecular markers of cell proliferation along with traditional clinical and morphologic characteristics can be used for differential diagnostics of ovarian tumors.**

***Key Words:* ovarian adenocarcinoma, tumor grade, Ki-67, p53, p21$^{WAF1/CIP1}$ and p16^{INK4a} expression.**

Nowadays etiology and pathogenesis of ovarian cancer (OC) remain still unclear. The risk factors of this pathology include age and peculiarities of reproductive function, hormone factors, especially estrogens and progesterone level, harmful environmental influence [1].

Many of current studies focus on the involvement of oncogenic viruses (the Epshteine-Barr virus, Human Papilloma virus type 16, 18, 48, 56, Herpes virus, Cytomegalovirus and TT-virus) and bacterial infections (*Chlamydia trachomatis, Mycoplasma spp., Ureaplasma urealiticum*) in the occurrence of epithelial ovarian tumors [2].

Besides, referred above such genetic factors as function of tumor suppressor genes and DNA reparation genes play an important and maybe the main role in OC origin [3]. Application of molecular-biological methods into oncology contributed to forming the concept about presence of certain expression profile in tumors of different origin. Recently, a group of ovarian tumors with high cell cycle genes expression was distinguished. According to the literature data, about 80.0% of hereditary OC forms are accompanied by alterations in *BRCA1* and *BRCA2* genes (in some cases in both genes simultaneously), which are caused by germline and somatic mutations, loss of heterozygosity or aberrated methylation of CpG islands in promotor region [4]. Methylation of CpG islands is proved to be one of the main ways of inactivation of suppressor genes in OC [5].

Many authors showed that mutation of *TP53* tumor suppressor gene is the most frequent genetic feature in sporadic cancer forms (about 50.0% of cases) [3]. The number of cases with mutated *TP53* among ovarian serous carcinomas and endometrioid malignant tumors is 57.0% and 25.0% respectively with maximum value in poorly differentiated tumors in patients with III or IV stage of disease. Ovarian serous carcinomas have mutated *TP53* gene even at the initial stage of illness. The missense mutation in specific DNA-binding domains leads to cancer development in the most cases because of the loss of normal p53 function. When wild type and mutated alleles of *TP53* gene are both present in the cell, the respective products may form an oligomeric protein complex. This phenomenon is called "dominant-negative effect of *TP53* mutation" [6]. In this case, wild type p53 can be only partly inactivated and detected by immunohistochemistry. Another type of *TP53* mutation resulting in the loss of gene's functional activity is premature stop codon (nonsense mutation). Protein products of such genes cannot be detected by immunohistochemistry [7].

One of the main p53 effectors is p21$^{WAF1/CIP1}$ gene — the cyclin-dependent kinases inhibitor from CIP/KIP family. The product of this gene is p21$^{WAF1/CIP1}$ protein, which is able to inhibit proliferation during almost all cell cycle phases (G1, S and G2). The p21$^{WAF1/CIP}$1 protein is activated by p53 protein encoded by wild, but not mutant TP53 type. From other hand, the increase of p21$^{WAF1/CIP1}$ expression under the presence of mutant TP53 can evidence on p53-independent pathway of regulation of p21$^{WAF1/CIP1}$ expression (e. g. by the protein products of *BRCA1, WT1, TP63* genes or by progesterone) [8–10].

Some researchers considered that the changes in *p16^{INK4a}* gene functions have great significance in OC pathogenesis as well [11–13]. The mutations of this gene usually appear on the early stages of transformation of ovarian epithelium [14]. First of all, the occurrence of neoplasia is caused by deletion in 9q21 region, where *p16^{INK4a}* gene is located and by hypermethylation of *p16^{INK4a}* promotor region. If the mutant gene is heterozygous, another allele, which is not mutated, continues to work as suppressor and the cell can function without abnormalities for a

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Abbreviations used: PI – proliferation index; LI – labeling index; OC – ovarian cancer.

while. However, hypermethylation of even one allele of *p16^{INK4a}* gene makes cell be susceptible to malignant transformation. Loss of *p16^{INK4a}* inhibitory function occurs in 40.0% of serous and 17.0% of mucinous ovarian tumors and is more likely for tumor cells with wild type *TP53 (*approximately 50.0% of tumors have wild type and 26.0% mutant *TP53*) [11, 12].

As ovarian epithelial cells undergo transformation, there are not only alteration in *TP53* suppressor gene, but abnormalities of regulator cell cycle genes as well (*p16^{INK4a}, p21$^{WAF1/CIP1}$, p27^{KIP1}, p14^{ARF}* and others).

Taking into consideration all mentioned data, the aim of our study was to investigate the p53, p21$^{WAF1/CIP1}$, p16^{INK4a} and Ki-67 expression in serous ovarian carcinomas of different grade.

MATERIAL AND METHODS

In the study, the surgical material of 43 patients with OC of I–IV stages was used. The age of the patients ranged from 41 to 76 years, with a mean value of 51.3 ± 2.0. The unaltered epithelial ovarian tissue from 8 women with mean age 53.3 ± 3.3 (45–75 years old), which underwent surgery for uterine fibromyoma, was used as relative control. All patients were cured in the Department of Oncogynecology, Institute of Oncology, AMS of Ukraine (the Head of the Department is prof. L.I. Vorobyova). The informed consent of all patients has been received.

Processing of operation material, immunohistochemical detection and evaluation of biomarkers expression and statistic analysis of obtained results were accomplished according to the standard procedure [15, 16] with modifications of our laboratory [17]. Histologic diagnosis was performed according to the criteria of the World Health Organization [18].

The operation material was fixed in 10% neutral formalin solution and processed for embedding in paraffin wax. The histologic diagnosis was verified by studying hematoxylin & eosin stained sections. The immunohistochemical detection of biomarkers was conducted using monoclonal primary antibodies (DakoCytomation, Denmark): anti-Ki-67 — MIB-1 clone; anti-p53 — DO-7 clone; anti-p21$^{WAF1/CIP1}$ — SX118 clone and anti-p16^{INK4a} — CINtec^{tm} clone. Reaction was visualized by EnVision system with next DAB staining. Cell nuclei were conterstained by Mayer's hematoxylin.

The results of immunohistochemistry were evaluated semiquantitatively via calculation of positively stained cells (labelling index — LI). The expression of markers was evaluated in 600–2000 tumor cells. The statistic method of median (Me) determination for each single parameter was used for correct interpretation of evaluation of the biomolecular markers expression. We have found that p21$^{WAF1/CIP1}$ median is 7.0%, p16^{INK4a} = 10,0% and p53 = 30.0%. According to these results the criteria for evaluation of markers expression were the following: the protein expression level was considered as low if LI < 10.0% for p53 and p16^{INK4a}, and if LI < 7.0% for p21$^{WAF1/CIP1}$; and as high if 10.0% ⩽ LI < 30.0% for p53, 10.0% ⩽ LI < 20.0% for p16^{INK4a} and 7.0% ⩽ LI < 15.0% for p21$^{WAF1/CIP1}$. The criteria for protein overexpression were LI ⩾ 30.0% for p53; LI ⩾ 20.0% for p16^{INK4a} and LI ⩾ 15.0% for p21$^{WAF1/CIP1}$. The proliferative potential was determined according to the number of Ki-67-positive cells: PI < 10.0% — low proliferative activity, PI ⩾ 10.0% — high level of proliferation.

RESULTS

By histologic differentiation, adenocarcinomas were subclassified into Grade I (G1, n = 8), Grade II (G2, n = 15) and Grade III (G3, n = 20). Immunohistochemical investigation showed a lack of Ki-67, p53, p21$^{WAF1/CIP1}$ and p16^{INK4a} expression (except some cases) in epithelial cells of ovarian normal tissue. In contrast to normal tissue, the expression of these markers was observed in the most of ovarian carcinomas (Table 1).

Table 1. The level of expression of biomolecular markers in ovarian adenocarcinomas with different histologic grade

Pathohistological diagnosis	The number of patients	The number of positive cells, %			
		Ki-67	p53	p21$^{WAF1/CIP1}$	p16^{INK4a}
Unaltered ovarian tissue	8	1.0 (1 case)	0	0	5.0 (1 case)
Adenocarcinomas	43	30.0 ± 0.3 (18.0–76.3)	40.3 ± 0.3 (6.7–72.5)	6.8 ± 0.3 (0–31.3)	31.1 ± 0,6 (0–66.7)
G1	8	14.0 ± 0.4 (18.0–28.8)	34.9 ± 0.7 (22.8–38.6)	9.4 ± 0.8 (0–31.3)	11.0 ± 0.8 (0–34.5)
G2	15	32.4 ± 0.5 (18.0–58.7)	37.0 ± 0.5 (12.6–70.0)	8.1 ± 0.8 (0–28.2)	27.0 ± 0.8 (0–42.2
G3	20	37.1 ± 0.4 (20.9–76.3)	45.8 ± 0.5 (6.7–72.5)	3.4 ± 0.3 (0–11.0)	35.9 ± 0.3 (0–66.7)

As shown in Table 1, proliferative potential of malignant ovarian tumors as well as p53, p16^{INK4a} expression were high. Meanwhile the level of p21$^{WAF1/CIP1}$ expression was low (Figure). With lowering of degree of differentiation ovarian tumor the quantity of proliferating cells increased. Similarly, the increase of the quantity of p53 and p16^{INK4a} positive cells was detected in less differentiated ovarian tumors. At the same time the percentage of cells with p21$^{WAF1/CIP1}$ expression in G1 and G2 ovarian adenocarcinomas was low and decreased significantly in G3 tumors (up to 3, 4%).

Expression of some biomolecular markers in OC tumors of certain histologic grade is shown in Table 2.

Table 2. Expression of biomolecular markers in OC tumors of different grade

The expression level of biomolecular markers	Ovarian adenocarcinomas (the number of cases, %)	The grade of differentiation (the number of cases, %)		
		G1	G2	G3
p53				
Low	7.3	0	6.7	11.1
High	19.5	25.0	33.3	5.6
Overexpression p21$^{WAF1/CIP1}$	73.2	75.0	60.0	83.3
Low	66.7	60.0	62.5	72.7
High	25.0	20.0	25.0	27.3
Overexpression p16^{INK4a}	8.3	20.0	12.5	0
Low	25.0	75.0	20.0	9.1
High	8.3	0	10.0	9.1
Overexpression Ki-67	66.7	25.0	70.0	81.8
Low	11.6	37.5	13.3	0
High	88.4	62.5	86.7	100.0

The most of ovarian adenocarcinomas (88.4%) were high-proliferating tumors. The p53 expression was ob-

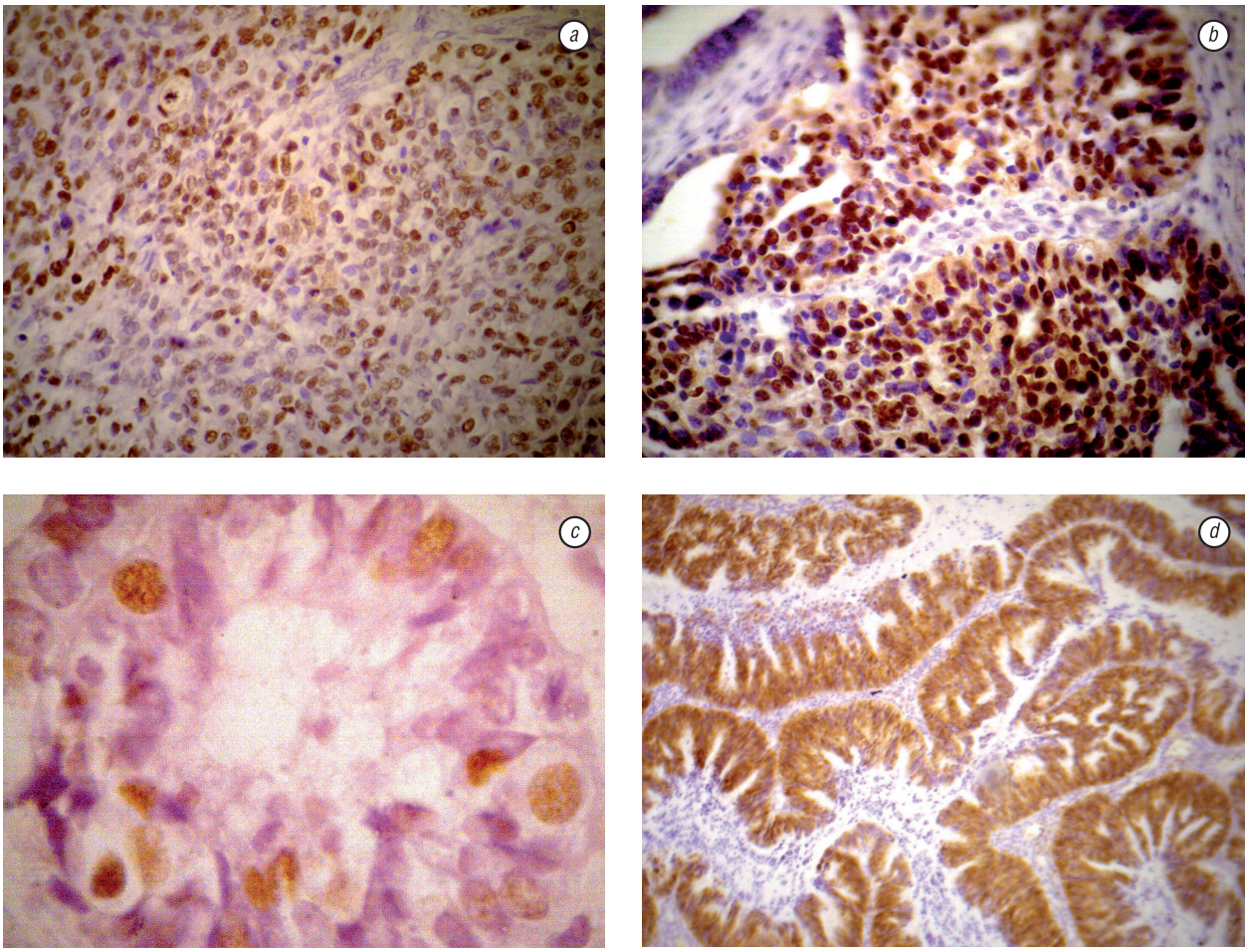

Figure. Immunohistochemical detection of expression of Ki-67 in G3 (*a*), p53 in G3 (*b*), $p21^{WAF1/CIP1}$ in G2 (*c*) and $p16^{INK4a}$ in G1 (*d*) serous ovarian adenocarcinomas. Original magnification x 400 (*a, b, d*) and x 900 (*c*)

served in 100% of ovarian tumors and was mainly high and very high (in 92.7% of investigated tumors).

The expression of $p21^{WAF1/CIP1}$ protein was revealed in 64.0% of tumors, but the high expression level was detected only in 25.0% and overexpression — in 8.3% of cases. The $p16^{INK4a}$ expression was determined in 84.0% of ovarian tumors and its overexpression was prevalent (66.7% cases). It is necessary to mark the inverse relation between biomolecular markers overexpression and the grade of ovarian adenocarcinomas differentiation.

The decrease of a histologic grade of ovarian tumor cells was associated with increase in quantity of cases with p53 and $p16^{INK4a}$ overexpression and high level of proliferative activity, reaching the maximum in G3 (83.3, 81.8 and 100%, respectively). In contrast to it, the number of cases with $p21^{WAF1/CIP1}$ overexpression was the highest in G1, decreased in G2 and wasn't revealed in G3 tumors.

DISCUSSION

The results of our research have revealed that the malignant ovarian tumors are characterized by the significant proliferative activity and level of p53 and $p16^{INK4a}$ expression. At the same time these tumors were characterized by low $p21^{WAF1/CIP1}$expression. The maximal values of Ki-67, p53 and $p16^{INK4a}$ and the minimal values of $p21^{WAF1/CIP1}$ expression were determinated in G3 ovarian tumors. It is possible that such decrease of $p21^{WAF1/CIP1}$ expression may be a result of a lack of transactivating influence of p53 protein on *p21*$^{WAF1/CIP1}$ gene. Summing up the carried out research, it is necessary to mark that the changes of expression of studied proteins, which were determined by us, coincided with the data of other authors [9,13]. In those studies were described that p53-dependent pathway of $p21^{WAF1/CIP1}$ activation is preserved only in clear cell and endometrioid ovarian carcinomas but disrupted in the most serous carcinomas, presumably associated with the loss of normal p53 function. In other words, in serous ovarian carcinomas the activation of *p21*$^{WAF1/CIP1}$ gene occurs by p53-dependent pathway and expression of $p21^{WAF1/CIP1}$ protein determinates the activity of Cdk complex — D1-D3/Cdk4, Cdk6 and proliferative potential of ovarian cancer, at the same time the high proliferative activity in ovarian tumors caused by the low level of $p21^{WAF1/CIP1}$ expression [10]. This conclusion is in line with our finding that G3 tumors with a high level of p53 accumulation express $p21^{WAF1/CIP1}$ at low levels. It has been shown that the patients with $p21^{+}p53^{-}$ phenotype have more favorable prognosis than the patients with $p21^{-}p53^{+}$ phenotype, and the determination of $p21^{WAF1/CIP1}$/p53 phenotype is better prognostic characteristics in patients with ovarian cancer than separate determination of level of these markers expression.

One more reason for derangements of $p21^{WAF1/CIP1}$ and p53 proteins functioning can be *BRCA1* gene

mutations (trans-activator of *TP53* and *p21*$^{WAF1/CIP1}$ genes), which are frequent event in hereditary ovarian cancer. Although they have generally been considered to have more limited roles in sporadic ovarian cancer there are data according to which the mutations at both genes *TP53* and *BRCA1*, which are associated with a decrease of *BRCA1* expression in sporadic ovarian cancers are observed [19]. On the other hand, several reports have focused on cell signal cascades, which occur with *TP53* participation and are often interrelated with signal pathways that are regulated by *RB* gene. Mutative events or changes of pathways of *TP53* and *RB* are observed in more than 80% of malignant tumors [20]. It is known that some factors can cause the *RB* inactivation: partial loss of heterozygosity of *RB*-locus, the increase of expression of cyclins and cyclin-dependent kinases of serous tumors of ovary is associated with *p16*^{INK4a} gene overexpression, probably reflecting accumulation of inactive *p16*^{INK4a} products [12]. It can be a result of carcinogenic action of Herpes and Human Papilloma (HPV) viruses since viral infection contributes to significant increase of *p16*^{INK4a} expression [2]. At the same time there were data about one more mechanism of simultaneous suppression of pRb, p53 and p21$^{WAF1/CIP1}$ proteins by formation of inactivating complexes between them and E6, E7 HPV oncoproteins (for 16 and 18 HPV types) [22]. The functional inhibition of Cdk' inhibitors by viral oncoproteins may allow these viruses to promote constitutive activation of cyclin-Cdk complexes and cell cycle progression. The E6 protein binds and inactivates p53 and E7 — pRb protein that can cause the proteolytic degradation of these suppressors and release of E2F transcriptional factor. E7 destabilizes pRB by induction its degradation via an ubiquitin-proteosome pathway. E2F can activate *p16*$^{MTS/INK4a}$ gene transcription and cause sudden increase of p16^{INK4a} expression. Besides, E7 can also bind and inactivate Cdk inhibitors p21$^{WAF1/CIP1}$ and p27^{KIP1}, thus providing another mechanism through which E7 can disrupt these cellular processes. E7 also interacts indirectly with cyclin E-Cdk2, mediated through p107, pRb-related proteins. The significant distinctions of p53 and p21$^{WAF1/CIP1}$ expression were observed in HPV16-positive and negative tumors in patients with breast cancer [23]. It has been shown that the level of p53 and p21$^{WAF1/CIP1}$ expression was significantly lower (or was absent) in the most of HPV16-positive carcinomas and on the contrary — HPV16-negative tumors had mainly high expression level of p53 and p21$^{WAF1/CIP1}$ proteins. Considering the fact that these viral oncoproteins inactivate and degrade the p53 and p21$^{WAF1/CIP1}$ proteins, these data indicate the resistance of p53 mutant protein to HPV16 action.

In conclusion, our present data demonstrate that Ki-67, p53, p21$^{WAF1/CIP1}$ and p16^{INK4a} proteins are differently expressed in normal ovarian surface epithelium and ovarian serous adenocarcinomas, that can be used for differential diagnostics of ovarian malignant process.

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ЭКСПРЕССИЯ БЕЛКОВ p53, $p21^{WAF1/CIP1}$, $p16^{INK4A}$ И Ki-67 В СЕРОЗНЫХ ОПУХОЛЯХ ЯИЧНИКА

Цель*: анализ экспрессии белков p53, $p21^{WAF1/CIP1}$, $p16^{INK4a}$ и Ki-67 в серозных опухолях яичника разной степени дифференциации.** ***Материалы и методы: **иммуногистохимическое определение уровня экспрессии белков Ki-67, p53, $p21^{WAF1/CIP1}$ и $p16^{INK4a}$ в образцах операционного материала 43 больных раком яичника и 8 пациенток с фибромиомой матки, эпителиальная ткань яичника которых не изменена.** ***Результаты:*** **установлено, что в неизмененном поверхностном эпителии яичников экспрессия белков Ki-67, p53, $p21^{WAF1/CIP1}$ и $p16^{INK4a}$ не выявлялась. Для серозных аденокарцином характерна высокая пролиферативная активность (индекс пролиферации (ИП) Ki-67 = 30,0 ± 0,3%), гиперэкспрессия p53 (индекс метки (ИМ) = 40,3 ± 0,3%) и $p16^{INK4a}$ (ИМ = 31,1 ± 0,6%), а также низкий уровень экспрессии $p21^{WAF1/CIP1}$ (ИМ = 6,8 ± 0,3%). Установлена зависимость уровня экспрессии изученных маркеров от степени дифференцировки серозных опухолей яичника: максимальный уровень экспрессии Ki-67, p53 и $p16^{/INK4a}$ и минимальный $p21^{WAF1/CIP1}$ отмечали в низкодифференцированных аденокарциномах яичника. Таким образом, низкий уровень экспрессии белка $p21^{WAF1/CIP1}$ (ИМ < 7,0%) с одновременной гиперэкспрессией $p16^{INK4a}$ можно считать фактором неблагоприятного течения серозного рака яичника.** ***Выводы:*** **результаты проведенного исследования показали, что молекулярно-биологические маркеры пролиферации клеток наряду с традиционными клиническими и морфологическими характеристиками могут быть использованы для дифференциальной диагностики опухолевого процесса в яичнике.**

Ключевые слова: **рак яичника, степень дифференцировки, экспрессия биомолекулярных маркеров, Ki-67, p53, $p21^{WAF1/CIP1}$ и $p16^{/INK4a}$.**