Frequency and characteristics of family cancer syndrome in ovarian cancer patients

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The aim of the study: **to assess the results of clinical, clinical-genealogical and molecular-genetic examination of OC patients and to substantiate its role as an important step for creation of genetic risk groups of developing neoplasia in the family.**
***Materials and methods*. The results of comprehensive clinical, clinical-genealogical and molecular-genetic examinations of 158 patients with OC, stage I–IV are presented. It was found that in probands' families (OC patients) malignant tumors of female reproductive system, gastro-intestinal tract and other were prevailing that conform to Lynch syndrome type II (family cancer syndrome).**
***Results*. Among the tumors of female reproductive system ovarian cancer was diagnosed in 27.5%, breast cancer – in 16.1%, uterine cancer – in 8.1%, and tumors of gastro-intestinal tract – in 20.2% of cases. Accordingly to family trees data cancer was more common in proband's mothers (35.5%), grandmothers (29.9%), and aunts (11.6%), and male relatives (19.8%). Molecular-genetic examination of genomic DNA of peripheral blood revealed 5382insC mutation in *BRCA1* gene in 9 patients with serous OC, 5 from them had family cancer syndrome. Mutation 6174delT in *BRCA2* gene in this clinical material was not detected. Germinal mutations in indicated suppressor genes are predictive factors of neoplasia development in family and proband's progeny and suggest the phenomenon of genetic predisposition to cancer development in the family.**
***Conclusions*. Family cancer history that is determined by clinical-genealogical analysis of the family is an important component in diagnostics of hereditary/non-hereditary variants of OC and creation of genetic risk groups for cancer development in the family with family cancer syndrome. Germinal mutation *5382insC* in the gene *BRCA1* is a predictive factor of neoplasia development in proband's progeny and suggests the phenomenon of genetic predisposition to cancer development in the family. Clinical-genealogical examination can be assessed as an integral part of diagnostic and preventive work of gynecologists, oncogynecologists and oncogenetics.**
Key words*: ovarian cancer, family cancer syndrome, mutations in BRCA1 and BRCA2 genes.*

Despite the introduction into clinical practice of new cytostatic drugs and treatment regimens, as well as modifications of increased resectability of tumors in ovarian cancer (OC) patients [1–3], the latter continues to attract the attention of not only oncologists, but morphologists and genetics as well. This is associated with its not conclusively established pathogenesis, asymptomatic initiation and aggressive course of tumor disease that leads to frequent cancer relapses within abdomen and prompt patients' death. Profound fundamental OC studies in the National Cancer Institute indicate that the survival rate of 32.3% of patients with newly diagnosed cancer is less than one year that indicated late diagnostics of tumor process due to inadequacy of early OC diagnostics and lack of risk groups of ovarian pathology development [4]. Above-mentioned substantiated the urgent need for further investigations in the context of determination of risk criteria and preclinical course of OC.

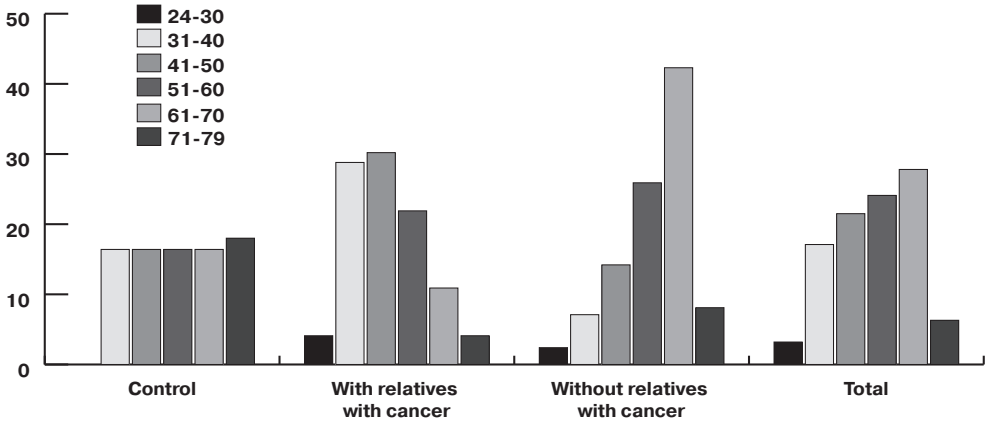
Current stage of oncology development is characterized by the increasing introduction of genetic research into practice, at that a number of papers indicated the relation of genetic alterations in tumor cells with clinical peculiarities of tumor process and patients' survival. This poses actual issues regarding possibility of application of molecular-genetic tumor peculiarities for oncogynecology purposes [5–7], in particular, for the assessment of the role of mutations expression in the genes – suppressors of tumor growth *BRCA1* і *BRCA2* in disposition to OC development, and also as factors that may be associated with neoplastic growth initiation in ovaries and characteristics of tumor process.

Addressing these issues may be positive when directing efforts of oncogynecologists towards creation of genetic risk group for OC basing on examination of cancer incidence in the family of oncologic patient that in literature is known as family cancer history. The rationale for such research is a well-known concept that germinal mutations account for the development of hereditary and family forms of cancer. As for germinal mutations, they are inherited, and every cell of the organism to which the germinal mutation was passed will have genetic alterations that reflect genomic instability of a new organism. Currently the most explored such genetic alterations are germinal mutations in the genes *BRCA1* and *BRCA2*. Its presence determines predisposition to OC and BC development, generally, at the age before 50, at that these cancer types may develop in several family members and in future generations [7–9]. In such families tumors of other organs also may develop (synchronous or metachronous), as well as bilateral tumors in paired organs that fits into the framework of Lynch syndrome – or primary-multiple tumors [10].

The aim of the study: to assess the results of clinical, clinical-genealogical and molecular-genetic examination of OC patients and to substantiate its role as an important step for creation of genetic risk groups of developing neoplasia in the family.

MATERIALS AND METHODS

Study materials were the results of complex (clinical, morphological, clinical-genealogical, molecular-genetic) examination of 158 patients with OC stage I–IV that were entered in the forms which we developed. Clinical-genealogical examination comprised analysis of the results of direct oncogynecologist's interview with proband (proband – a patient for whom the family tree, based on her clinical-genealogical data, was built). During the interview the number of relatives suffering from cancer in I–III generations and family relations of these persons to the proband were estimated. Clinical-genealogical data were analyzed according to II Amsterdam criteria: three or more relatives with Lynch-associated tumors (OC, uterine cancer (UC), stomach cancer, colorectal cancer, others), at that one of oncologic patients has first degree of kindred with other patients, and cancer is observed, at least, in two generations. Special attention was paid to the patients who developed cancer at the age <50 years. Clinical-genealogical analysis of family trees was provided in 158 patients with OC stage I–IV. As a control the molecular-genetic studies were provided in 55 healthy women which family trees did not have relatives with cancer in three generations.



Distribution (%) of OC patients by age comparing with control (healthy women) and clinical-genealogical data

Basing on complex proband's examination according to the standards of examination of patients with cancer of female reproductive organs, adopted in Ukraine, tumor process spread within the ovary was determined according to FIGO classification. Histological examination of excised ovarian tumors was provided with determination of histological type and OC grading.

All OC patients received complex treatment according to generally accepted standards of Ukraine (order of the MOHC No. 554 dated 2007). At the first stage surgical treatment was provided to the extent of panhisterectomy and omentectomy (at OC stage I–II), or cytoreductive surgery in optimal volume in patients with OC stage III (panhisterectomy, omentectomy, residual metastases through pelvic peritoneum and abdominal cavity, not exceeding 1.0 cm in diameter) or suboptimal cytoreductive surgery (in the same volume, provided that residual metastatic lesions on peritoneum did not exceed 1.0 cm in diameter). Further all the patients received 6 courses of adjuvant polychemotherapy (PCT) with the schemes «CC» (cyclophosphan+carboplatin) or «TC» (taxanes+carboplatin). Every 6 months ultrasound examination of small pelvis organs and abdominal cavity was provided, radiological examination of thoracic organs was performed once a year and, if necessary, CT of small pelvis organs, abdominal and thoracic cavities, lymph nodes, and brain was provided.

All the patients received hospital-based treatment in CE «Cherkassy Regional Oncologic Dispensary» of Cherkassy Regional Council and gave written consent to use their biological material for research purposes.

The material for morphological examination was presented by excised ovarian tumors, for molecular-genetic examination – by peripheral blood which was collected before patients' treatment. Genomic DNA was isolated from it and subjected to further molecular-genetic examination for identification of *185delAG* and *5382insC* mutations in *BRCA1*gene, *617delT* mutations in *BRCA2* gene, using modified protocols with oligonucleotide primers with application of allele-specific polymerase chain reaction (PCR). Specific fragments of *BRCA1* and *BRCA2* genes were amplified using commercial kit DreamTaq Green PCR Master Mix («Thermo Scientific», USA). State of amplified fragments was analyzed in 2.5% agarose gel (agarose of the company «Thermo Scientific», USA) with addition of ethidium bromide, molecular weight marker GeneRuler 50 bp DNA Ladder («Thermo Scientific», USA) and subsequent visualization by computer program Vitran. We express our sincere acknowledgment for the help in molecular-genetic experiments to candidate of med. sci. Z.I. Rossokha (SE «Reference centre for molecular diagnostics of the Ministry of Public Health of Ukraine»). Study results were assessed with statistic methods: evaluation of Student's criterion t and Yule's association coefficient.

RESULTS AND THEIR INTERPRETATION

Depending on clinical-genealogical data 158 patients with OC (probands) were divided into 2 groups: with/without relatives with cancer of any localization. It was found that malignant tumors were in relatives of 73 (46.2%) probands, whereas 85 (53.8%) probands did not have relatives with cancer.

Age of probands and females of control group ranged from 24 to 79 years. More detailed distribution of examined persons is presented in the Picture, which demonstrates that, in general, increase in number of probands, aged from 30, is seen. If we con-

Table 1

Distribution of probands (OC patients) according to clinical-pathological characteristics of tumor process

Characteristics		Group 1 Number of probands who had relatives with cancer in their family trees, n=73/100%		Group 2 Number of probands who did not have relatives with cancer in their family trees, n=85/100%		Total probands, 158/100%
		n	%	n	%	n / %
OC stage according to FIGO classification	I	19	26.0	32	37.6	51/32.3
	II	7	9.6	9	10.6	16/10.1
	III	45	61.6	41	48.3	86/54.4
	IV	2	2.7	3	3.5	5/3.2
Tumor morphology: – serous papillary OC		64	87,7	80	94.1	144/91.1
– other morphological forms		9	12,3	5	5.9	14/8.9
Histological grade of OC	G1	32	43.8	45	52.9	77/48.7
	G2	18	24.7	22	25.9	40/25.3
	G3	23	31.5	18	21.2	41/26.0

Table 2

Localization and frequency of malignant tumors in probands' relatives with cancer

Diagnosis		Number of proband's relatives with cancer	
		n	%
Cancer of organs of female reproductive system	OC	41	27.5
	BC	24*	16.1
	UC	12	8.1
Cancer of gastro-intestinal tract	CC	26	17.4
	GC	18	12.1
	PC	1	0.7
Lung cancer		22	14,8
Prostate cancer		2	1,3
Other tumors		3	2,0
Total		149	100,0

Note. OC – ovarian cancer, BC – breast cancer, UC – uterine cancer, CC – colon cancer, GC – gastric cancer, PC – pancreatic cancer.
* – one patient had bilateral BC.

Table 3

Distribution of relatives who had cancer of female reproductive system organs, stomach and colon according to family kinship with proband

Diagnosis	Grandmother, n=35/100/%	Mother, n=43/100%	Sister, n=5/100%	Children	Aunt, n=14/100 %	Male persons, 24 /100 %	Totally patients, n/100%
OC	12/34.3	24/55.8	1*	-	4/28.6	-	41/33.9
BC	13/37.1	8/18.6	-	-	3/21.4	-	24/9.8
UC	1/2.9	2/4.6	4*	-	5/5.7	-	12/9.9
CC	2/5.7	6/14.0	-	-	1/7.1	17/70.8	26/21.5
GC	7/20.0	3/7.0	-	-	1/7.1	7/29.2	18/14.9
	35/29.9	43/35.5	5/4.1	-	14/11.6	24/19.8	121/100

Note. * – percents were not calculated due to small number of patients.

sider the age of probands on a case-by-case basis, i.e. depending on presence/absence of oncologic patients in family trees, mean age was 48.7±3.6 years (in case of relatives with cancer) and 59.1±3.8 years (absence of relatives with cancer). Namely, the age of the patients with association of malignant tumors in the family trees was 10.4 years less than the age of probands without relatives with cancer that is consistent with the literature data. Age mode and median in probands were also different. In probands with relatives with cancer the mode was 41–50 years, age median – 38 years, in probands without oncologic pathology in family trees – 61–70 years and 60 years, respectively ($p<0.05$). These data are important in terms that more early period of OC and BC manifestation is typical for hereditary cancer variants [11].

Distribution of probands according to clinical-pathological characteristics of tumor process in ovary demonstrated that majority of probands of both groups had OC stage 1 and III, whereas OC stage II and IV was in small number of patients.

Morphological examination of tumors showed that in 144 (91.1%) probands OC of serous genesis prevailed significantly, 87.7% and 94.1% for probands from groups I and II, respectively ($p>0.05$). Other histological forms (mucinous OC, granulocellular OC) were significantly less common (14/9.9%) in probands of both groups. Foresaid confirms literature data about higher occurrence and malignancy of serous cancer forms.

At cytomorphological assessment it was estimated that the majority of tumors were well-differentiated (G1). Analysis in individual groups of probands demonstrated that in probands of group I the number of G1-tumors was lesser (43.8%) than in group 2 probands (52.9%), while at the same time the number of G3-tumors was larger (31.5%), than in group 2 (21.2%). Number of G-tumors of moderate differentiation grade was almost the similar. Mathematic processing demonstrated weak association between number of patients with high and low differentiation grade that is indicated by Yule's coefficient (Ca=0.285).

Analysis of clinical-genealogical data in family trees of probands (OC patients) determined tumor processes polymorphism by localization and genesis (Tabl. 2).

It can be seen from the table that the most frequent were the tumors of female reproductive system organs that comprised together 77 (51.7%). Among them the first place belonged to OC (27.5%), second – to breast cancer (BC – 16.1%), third – to uterine cancer (UC – 8.1%). Significant rate of such tumors may be conditioned by common pathogenesis, in particular, by such factor as hormonal homeostasis disorder in the members of the same family that is manifested both on the level of clinical symptoms and by disorder of menstrual or fertility function. Second in frequency of oncologic pathology was cancer of gastro-intestinal tract organs, at that colon cancer (CC) was more common than gastric cancer (GC), 17.4 and 12.1, respectively; pancreatic cancer (PC) was only in one relative (0.7%). In addition, large number of patients had lung cancer (LC – 14.8%) Other tumors, including prostate cancer (PrC) were in small numbers of cases.

For more detailed characteristics of the results of clinical-genealogical examination of patients and for determination of hereditary OC variants we analyzed the frequency of relatives with cancer by their family kinship with proband, at that we paid attention only to the frequency of tumors of female reproductive system organs and gastro-intestinal tract that were seen

most commonly. As it is seen from the Tabl. 6, OC was the most frequent type in relatives: it comprised 55.8% in probands' mothers, slightly less in grandmothers (34.3%) and aunts (28.6%) that suggests hereditary disposition to OC. Similar trend of relatives' distribution is common with BC as well, its frequency was the largest in grandmothers (37.1%), lesser in aunts (21.4%) and mothers (18.6%). By contrast, UC in probands' families was rare – least of all in grandmothers (2.9%), then – in mothers (4.6%) and aunts (5.7%). Attention is drawn to the fact that probands' children did not have malignant tumors, although with our material we found out the presence of mutations in the genes BRCA1/2 in healthy daughters if their mothers suffered from OC. Regarding the cancer of gastro-intestinal organs, which total number in probands' relatives is also high, one should indicate CC prevailing over GC. These cancer types are found with different frequency in female and male persons, prevailing in male.

In general, the presence of such a broad range of tumors with different genesis indicates family cancer syndrome of Lynch syndrome II, at that in family members tumors of different localization develop. Such syndrome frequency in families of OC patients was 28/27.2%, syndrome OC/BC – 10.0%, hereditary OC – 7.7%. It was determined that in 10 family trees association of BC with CC was established that is one more evidence for Lynch syndrome II.

The main interest attracts the role of hereditary OC variants or OC as a part of family cancer syndrome in the context of tumor process state, in particular, regarding OC relapses. Considering the fact that we examined OC patients for the carriership of mutations *5382insC* in *BRCA1* gene and mutation *6174delT* in *BRCA2* gene, we conducted comparative analysis of relapses rate in examined patients, although general material does not provide with possibility to give ultimate answer to this question because the part of the patients finished treatment in 2015. The results demonstrated that the mutation *6174delT* in *BRCA2* gene was not found in any case. Mutation *5382insC* in *BRCA1* gene was diagnosed in 9 patients with serous OC, 5 of them had family cancer syndrome. At that, in case of family cancer syndrome, only one patient did not have relapses in 2 years, whereas 4 patients had both early and late relapses of tumor process. In patients without family cancer syndrome early relapses were not diagnosed, all the patients are followed.

Due to the small number of examined persons we cannot give the clear answer to the question – whether worse/better clinical course of OC in patients with mutations in *BRCA1* and *BRCA2* genes is seen. This issue is vigorously debated in the literature. On the one hand, the majority of researchers detect mutations in indicated genes in 10% of patients with family OC or BC [12]. According to [13], the analysis of genetic alterations in the genes *BRCA1* and *BRCA2* in 82 families with family OC in Japan revealed 45 families with carriers of germinal mutations in the genes *BRCA1* and *BRCA2*. Large proportion of the mutations was seen in patients with family serous OC, it depended on tumor process spread, but did not depend on patients' age.

Meta-analysis of publications about the role of mutations in the genes *BRCA1/2* in survival and duration of relapse-free period demonstrated that carriers of mutations in these genes have better clinical characteristics than non-carriers, although in patients with BC carriers of mutations in *BRCA1* gene had worse survival rates [7]. Heterogeneity of opinions regarding the role of mutations in the genes *BRCA1* and *BRCA2* is explained by novel data which suggest that in predisposition to OC and BC development, besides indicated mutations, the mutations in other genes (*CHEK2, ATM, PALB2*) are involved that functionally interact with genes-suppressors [14–15].

It is evident that just examination of mutations in the genes *BRCA1* and *BRCA2* and their relation with other genes mutations will give the possibility to substantiate the meaning of genetic alterations in two recently specified categories of OC – type I and type II, each of them is characterizes with specific clinical-pathological features [16, 17]. Meanwhile, the role of family anamnesis of OC patients remains important and essential for diagnostic and preventive medicine. The number of papers declare that family cancer history has significant value for determination of association of malignant and benign tumors as part of different syndromes or in a form of hereditary cancer variants, therefore clinical-genealogical analysis of family trees, according to some authors' opinion, should become an integral part of gynecological and oncogynecological practice [18–20].

From our point of view both clinical-genealogical examination and determination of hereditary/non-hereditary variant of OC and other hormone-dependent tumors, and genetic testing of the mutations in the genes *BRCA1, BRCA2* extends individual tumors' characteristic, regarding their pathogenesis, and role of germinal genetic alterations as causal factor of malignant transformation. In addition, it provides with clear idea of the possibility of assessment of predictive neoplasia development in proband's family [21, 22]. The latter in an important step in cancer prevention through creation of genetic risk groups, in particular, for the development of OC and hormone-dependent forms of oncologic pathology. Integration of family cancer history and molecular biology of tumors will allow for more precise understanding of individual tumor process, heterogeneity of genetic alterations that is necessary for the development of both individual preventive measures, and treatment and monitoring of such patients and their families members.

CONCLUSIONS

1. The results of complex clinical, clinical-genealogical and molecular-genetic examination indicate that in families of 46.2% of probands (OC patients) malignant tumors, mainly of female reproductive system organs (OC, BC. UC), gastro-intestinal tract (CC, GC) and others are found, that corresponds to Lynch syndrome type II (family cancer syndrome).

2. Most frequent tumors, registered in relatives, were the tumors of female reproductive system organs (51.7%) among them OC accounted for 27.5%, BC – for 16.1%, UC – for 8.1%, and tumors of gastro-intestinal tract – for 20.2%. According to family trees data cancer was more common in proband's mothers (35.5%), grandmothers (29.9%), and aunts (11.6%), and also male relatives (19.8%).

3. Serous OC prevailed in probands. Weak association between number of patients with low and high grade malignancy was seen (Yule's coefficient of association was 0.285).

4. Molecular-genetic study of genomic DNA of peripheral blood determined mutation *5382insC* in the gene *BRCA1* in 9 patients with serous OC, each from them had family cancer syndrome. Mutation *6174delT* in the gene *BRCA2* in this clinical material was not detected.

5. Family cancer history that is determined by clinical-genealogical analysis of the family is an important component in diagnostics of hereditary/non-hereditary variants of OC and creation of genetic risk groups for cancer development in the family with family cancer syndrome. Germinal mutation *5382insC* in the gene *BRCA1* is a predictive factor of neoplasia development in proband's progeny and suggests the phenomenon of genetic predisposition to cancer development in the family. Clinical-genealogical examination can be assessed as an integral part of diagnostic and preventive work of gynecologists, oncogynecologists and oncogenetics.

Частота и характеристика семейного ракового синдрома у больных раком яичника

О.В. Палийчук

Цель исследования: оценить результаты клинического, клинико-генеалогического и молекулярно-генетического обследования больных раком яичника (РЯ) и обосновать их значение как необходимого этапа для формирования групп генетического риска развития неоплазий в семье.

Материалы и методы. В статье представлены результаты комплексного клинического, клинико-генеалогического и молекулярно-генетического исследования 158 больных РЯ I–IV стадии. Установлено, что в семьях пробандов (больные РЯ) наблюдаются злокачественные опухоли преимущественно органов женской репродуктивной системы, пищеварительного тракта и другие, что обусловлено синдромом Линча II типа (семейный раковый синдром).

Результаты. Среди опухолей органов женской репродуктивной системы частота РЯ составляла 27,5%, частота рака грудной железы – 16,1%, рака тела матки – 8,1%, опухолей пищеварительного тракта – 20,2%. По данным родословных раком чаще болели матери (35,5%), бабушки (29,9%), тети (11,6%) пробандов и родственники мужского пола (19,8%). Молекулярно-генетическое исследование геномной ДНК периферической крови выявило мутации 5382insC в гене BRCA1 у 9 больных серозным РЯ, из которых у 5 был семейный раковый синдром. Мутация 6174delT в гене BRCA2 на данном клиническом материале не выявлена. Герминальные мутации в указанных генах-супрессорах являются предиктивными факторами возникновения неоплазии в семье и у потомков пробанда и свидетельствуют о феномене наследственной предрасположенности к развитию рака в семье.

Заключение. Семейная история рака, которая определяется путем клинико-генеалогического анализа заболеваемости членов семьи, является важным компонентом в диагностике наследственных / не наследственных вариантов РЯ и в создании групп генетического риска развития рака в семье с семейным раковым синдромом. Герминальная мутация 5382insC в гене BRCA1 является предиктивным фактором появления неоплазии у потомков пробанда и свидетельствует о феномене наследственной предрасположенности к развитию рака в семье. Клинико-генеалогические исследования можно расценивать как интегральную часть диагностической и профилактической работы гинекологов, онкогинекологов и онкогенетиков.

Ключевые слова: *рак яичника, семейный раковый синдром, мутации в генах BRCA1 и BRCA2.*

Частота та характеристика сімейного ракового синдрому у хворих на рак яєчника

О.В. Палійчук

Мета дослідження: оцінити результати клінічного, клініко-генеалогічного та молекулярно-генетичного обстеження хворих на рак яєчника (РЯ) та обґрунтувати їхнє значення як необхідного етапу для формування груп генетичного ризику щодо розвитку неоплазій у родині.

Матеріали та методи. У статті представлені результати комплексного клінічного, клініко-генеалогічного і молекулярно-генетичного дослідження у 158 хворих на РЯ I–IV стадії. Установлено, що у родинах пробандів (хворі на РЯ) спостерігаються злоякісні пухлини переважно органів жіночої репродуктивної системи, травного тракту та інші, що відповідає синдрому Лінча II типу (сімейний раковий синдром).

Результати. Серед пухлин органів жіночої репродуктивної системи частота РЯ становила 27,5%, частота раку грудної залози – 16,1%, раку тіла матки – 8,1%, пухлин травного тракту – 20,2%. За даними родоводів на рак частіше хворіли матері (35,5%), баби (29,9%), тітки (11,6%) пробандів та родичі чоловічої статі (19,8%). Молекулярно-генетичне дослідження геномної ДНК периферійної крові виявило мутацію 5382insC у гені BRCA1 у 9 хворих на серозний РЯ, з яких у 5 був сімейний раковий синдром. Мутація 6174delT у гені BRCA2 на даному клінічному матеріалі не виявлена. Гермінальні мутації у зазначених генах-супресорах є предиктивними факторами появи неоплазії у родині і нащадків пробанда і свідчать про феномен спадкової схильності до розвитку раку у родині.

Заключення. Сімейна історія раку, яка визначається шляхом клініко-генеалогічного аналізу родини, є важливим компонентом у діагностиці спадкових/не спадкових варіантів РЯ і створенні груп генетичного ризику щодо розвитку раку у родині з сімейним раковим синдромом. Гермінальна мутація 5382insC у гені BRCA1 є предиктивним фактором появи неоплазії у нащадків пробанда і свідчить про феномен спадкової схильності до розвитку раку у родині. Клініко-генеалогічні дослідження можна розцінювати як інтегральну частину діагностичної і профілактичної роботи гінекологів, онкогінекологів та онкогенетиків.

Ключові слова: *рак яєчника, сімейний раковий синдром, мутації у генах BRCA1 і BRCA2.*

Сведения об авторе

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