GENETIC FACTORS AND THEIR ROLE IN PREDISPOSITION TO FORMATION OF MULTIPLE PRIMARY MALIGNANCIES OF FEMALE REPRODUCTIVE SYSTEM

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SUMMARY

Clinical, clinical-genealogic and molecular-genetic studies were conducted in 47 patients (aged 23 to 83 years) with primary multiple primary malignancies (PMMs) of female reproductive system organs (FRSO) from the families, whose relatives (first and second genetic relationship) had cancer. Characteristics of synchronous and metachronous PMMs was presented, the later in 75% of patients developed after age of 50 years. Among metachronous tumors in patients with cancer of FRSO the most frequently diagnosed corpus uteri cancer (39.6%), ovarian cancer (20.8%), breast cancer (14.6%) that may indicate at common mechanisms of primary and secondary tumors pathogenesis. Results of clinical-genealogical study suggest hereditary disease character in probands: cancer family syndrome was determined in 12.8% of family trees with aggregation of different genesis tumors, in 6% - hereditary ovarian, corpus utery, breast cancer. According to the molecular-genetic studies results in 8 (18.2%) of 44 examined patients mutations *5382 insC* in gene *BRCA1* and *6174 del* in gene *BRCA2* were identified that may indicate the role of genetic factors in PMMs of FRSO development. Clinical-genealogical family analysis and mutations determination in genes-suppressors *BRCA1* and *BRCA2* should be viewed as integral part of complex survey in patients with FRSO cancer for determination of genetic risk of secondary

tumors and development of principles of genetic prevention of cancers in their relatives.

Key-words: Cancer of female reproductive system organs, primary multiple malignancies, family cancer syndrome, genes BRCA1 and BRCA2, mutations.

Introduction. Absence of downward tendency of cancer morbidity of female reproductive system organs (FRSO) substantiates increased attention to this problem. For its resolution are necessary new programs aimed at prevention and early diagnostics of malignancies, including those of primary multiple oncological pathology. Primary multiple malignancies (PMMs) refer to poorly characterized oncological pathology although interest to it appeared in the seventies of the recent century. Scientific research results concerning peculiarities of PMMs clinics and course are covered in serios of monographs and papers [1,14-18]. However notwithstanding many years of studies classification of these tumors, their complex clinical characteristics is absent up to nowadays due to diversity of histological types of PMMs, and also prevention principles were not developed, patients' monitoring tactics and risk groups for secondary tumors development after oncological patients treatment were not determined [11,13].

Clinical studies results suggest increase of PMMs incidence in the recent years that may be explained by number of reasons. First of all that may be associated with tumors diagnostics optimization due to introduction of new methods of patients examination (endoscopy and US, computer and magneto-resonance tomography, immuno-enzyme, immuno-morphological and molecular-genetic methods of surgical material examination). Besides this secondary tumors development is possible after oncological patients treatment, especially in young patients, after chemo- and radiotherapy application that have inherent mutagenic effect on body cells. Environmental hazards, labor conditions, immunodeficiency, life style – are also prerequisites for oncological pathology development, especially in elderly people, whose life span increases.

It is also necessary to mention substantial importance of hereditary factors in development of several tumors with different genesis that may be explained by pleiotropic action of mutant gene, which is passed from generation to generation [3,22,26]. PMMs take place in the presence of genetic predisposition to malignancies development that is specific to syndromes (Gardner, Lynch, Li-Fraumeni syndromes, syndromes of multiple endocrine neoplasias, increased spontaneous and induced chromosome fragility and others) [4,6]. Were described cases of secondary tumors development in patients with chronic lympholeucosis or lymphogranulomatosis, where pronounced immunodeficiency was observed [5]. According to the opinion of number of authors PMMs development in FRSO also is not casuistry [7,19,23,25,28,30], although its pathogenesis and development regularities remain uncertain.

PMMs according to terms of its development, are divided into synchronous and metachronous. Synchronous PMMs arise simultaneously with primary tumor or in half-year period after their diagnostics, and metachronous PMMs are diagnosed in different periods after 6-months term of verification of primary malignant process localization.

At PMMs diagnostics researchers are guided with criteria that were defined as long ago as in the thirties of the recent century. Major criteria that are widely used in clinical studies are the following: a) each of primary multiple tumors should be characterized by clear histological malignancy pattern, b) every tumor should be localized at some distance from one another, c) secondary tumor should not be metastatic lesion of the primary tumor. Study of PMMs clinical peculiarities allowed to specify these criteria: primary multiple tumors – are two and more tumors that developed in single organism; they have different or similar histogenesis, different biological potential (benign, malignant or its combination), different or similar histological structure; they are localized in the same organ (or in double organs) of the single system, in different organs of the same system, or in different organs of the different systems, and are detected simultaneously (synchronously), consecutively (metachronously), and in combined manner

(synchronously-metachronously, metachronously-synchronously); and also comply with rules that exclude possibility to consider secondary tumor as relapse or metastasis.

In the recent years our attention has been focused on the role of genetic factors in development of hereditary forms of FRSO cancer [9]. During analysis of clinical-genealogical data of patients with cancer of FRSO we paid attention to presence of PMMs in pedigries of patients with corpus uteri cancer **(CUC),** breast cancer (BC), ovarian cancer (OC) that allowed to segregate hereditary, family and sporadical cancer forms.

Aim of study: to present clinical-morphological characteristics of tumor processes and clinical-genealogical characteristics of patients with PMMs of female reproductive system organs.

Material and methods

We examined 47 patients with PMMs of FRSO from families, whose relatives (first and second genetic relationship) had cancer. Among 47 patients with PMMs in 14 patients primary tumor was breast cancer (BC), in 13 - CUC, in 7 – ovarian cancer (OC). Also 13 patients with colorectal cancer (CC) that had secondary tumors of FRSO were included into total number of examined persons. Benign neoplasias and also those tumors that had the same morphology and were localized at the same FRSO were excluded from the total number of neoplasias. All patients were examined and underwent treatment (surgical treatment, radio-, chemotherapy within the framework of complex and/or combined special treatment) according to existing standards of treatment in Ukraine, at Cherkassy Regional Cancer Center in 2005-2009, and the patients gave informed consent to use their clinical data for research purposes.

For all the patients the results of clinical, laboratory, instrumental examination and also clinical-genealogical data with specially designed questionnaire were analyzed; the latter was filled out during interview with patients to elucidate the number of relatives who had cancer and degree of their relationship with proband (probands – patients with primary multiple tumors).

During diagnostics of primary multiple tumors we were guided by clinical and pathomorphological criteria that were referred to in the Introduction to the publication. Clinical diagnosis was verified by morphological examination of excised tumors. Surgical specimen was subjected to classical histological processing followed by hematoxylin and eosin staining of histological sections and assessment of tumors morphology with microscope "Axiostarplus" ("Carl Zeiss") at magnifications 100-400.

Blocks of surgical specimens of 44 (93.6%) of 47 patients with PMMs of FRSO were selected from Cherkassy Regional Pathoanatomy Archive, on these blocks molecular-genetic study of the most common in Slavic population mutations in genes BRCA1 and BRCA2 was performed (Reference centre for molecular diagnostics of the MPHU of Ukraine, Kiev). The study included DNA isolation from tumors' histological sections, amplification of DNA fragments (allele specific and classic), and electrophoretic separation of amplification fragments in 1.5% agarose gel.

Results and discussion

According to the Cancer Register in Cherkassy Regional Cancer Center during 2010-2012 years 1012 PMMs patients of different gender were registered for dispensary recording. Among them were 580 (57.3%) patients females with PMMs of different genesis. From this number of patients in 193 (33.3%) PMMs of FRSO were diagnosed (tabl. 1, 2). How it is seen from the mentioned table PMMs of FRSO incidence during indicated years has not changed reliably, and it varied from 32.1 to 34.7% that may be explained by annual fluctuation of oncological morbidity in females.

Among PMMs the most common pathology was BC (53.9%); whereas CUC and OC incidence was smaller – 33.2 and 12.9%, respectively. Variability of tumors number in different years was noticed – it was 4.0% for BC, 7.7% for CUC and 4.3% for OC.

Table 1. PMMs patients incidence for years 2010-2012 (according to Cherkassy Regional Cancer Center data)

Indices	Patients number, n/%			
	2010	**2011**	**2012**	**Total**
Total number of females that were registered for dispensary recording	2322/32.7	2375/33.4	2406/33.9	7103/100
Total number of females – PMMs patients that were registered for dispensary recording	181/31.2	204/35.2	195/33.6	580/100
Total number of patients with PMMs of female reproductive system organs that were registered for dispensary recording	67/34.7	64/33.2	62/32.1	193/100

Table 2. Incidence of patients with PMMs of female reproductive system organs for years 2010-2012 (according to Cherkassy Regional Cancer Center data)

Indices	Patients number, n/%			
	2010	**2011**	**2011**	**Total**
Total number of BC patients that were registered for dispensary recording (primary tumor)	35/52.2	36/56.2	33/53.2	104/53.9
Total number of CUC patients that were registered for dispensary recording (primary tumor)	24/35.8	18/28.1	22/35.5	64/33.2
Total number of OC patients that were registered for dispensary recording (primary tumor)	8/11.9	10/15.6	7/11.3	25/12.9
Total	67/100	64/100	62/100	193/100

Clinical data analysis demonstrated that in 7 (14.9%) of 47 patients PMMs were synchronous, in 40 (85.1%) – metachronous. Generally, patients' age at diagnostics varied from 23 to 83 years, average age was 49.9±4.4 years, age

median – 50 years. Obtained data coincide with literature data. In that way, according to data [18], average age of patients with synchronous OC and CUC was 49 years, according to another data [22] – 47.3 years. More detailed patients' distribution according to age (Fig. 1) demonstrated that the largest patients' number with primary tumor (78.7%) was within the age range 31-60 years, with metachronous tumor (60%) - within the age range 51-70 years.

Calculations have shown that age of synchronous PMMs patients varied from 39 to 74 years resulting on average 57.6±5.6 years, age median was 57 years. Minimal metachronous PMMs patients' age was lesser (23 years), maximal age – was larger (83 years); at that average age (48.6±6.1 years) and median (50 years) demonstrated downward tendency ($p>0.05$) comparing to those in the group of synchronous cancer patients.

The period between diagnostics of primary and metachronous tumor was different and it varied from 3 to 27 years. The largest period (27 years) was in CUC patient (primary tumor at 50 years of age), later on in this patient 3 metachronous tumors developed (colon cancer, skin cancer, Hodgkin lymphoma).

According to the time of secondary tumor development (synchronous or metachronous) and morphological diagnosis of primary tumors all patients were divided into 4 groups: group 1 – BC patients (14), group 2 – CUC patients (13), group 3 – OC patients (7), group 4 – CC patients (13); and major clinical-morphological peculiarities were analyzed separately according to these groups. Clinical characteristics, clinical-genealogical study results, and morphological peculiarities of synchronous tumors are presented in the table 3.

Table 3. Results of clinical, morphological and clinical-genealogical studies in patients with primary multiple synchronous cancer (n=7)

Patients' groups and primary tumors characteristics				
Patients' groups	Group 1	Group 2	Group 3	Group 4
Primary tumors	BC	CUC	OC	CC
Patients' number	2	3	1	1
Patients' age	39, 54	53, 68, 74	58	57
Stage	I	Ia, Ib, Ib	3c	I
Pathomorphological	Ductal	Adenocarci	Serous	Mucinous

diagnosis	infiltrative scirrhus	noma	adenocarcinoma	cancer
Differentiation degree of tumors	G2, G1	G0, G1, G1	G3	G2
Secondary tumors in groups of patients with synchronous cancer				
Secondary tumors	CUC	OC (2), CC (1)	CUC	OC
Patients' number	2	3	1	1
Stage	Ia	Ic – 2b	Ib	2c
Differentiation degree	G0, G2	G2 , G2, G2	G1	G3
Pathomorphological diagnosis	Adenocar cinoma	Endomet-rioid, serous papillary cancer, Adenocarci-noma	Adenocarcinoma	Serous adenocar-cinoma
Malignant tumors in proband's relatives	BC – in sister, grandmot her	CUC in daughter and mother, BC in sister, CC in brother, LC (lung cancer) in grandfathers	BC in mother	CerC in sister

Note: CerC – cervical cancer.

How it is seen from the data synchronous tumor in BC patients was CUC, in CUC patients – OC and CC, in patient with OC – CUC, in patient with CUC – OC; at that according to clinical data all the patients were diagnosed with primary malignant process at the first disease stage. Synchronous tumors had different histological structure comparing with primary tumor, and in the majority of patients, excluding those with CC and OC, first diseases stage was also diagnosed. It is worth mentioning that in BC and CUC patients were also determined malignant tumors of the same or different genesis in relatives of first or second genetic relationship that corresponded to conception of family cancer syndrome (Lynch syndrome II) [19, 23].

Results of clinical, morphological, clinical-genealogical studies of patients with metachronous cancer are presented in the Table 4. PM patients' age varied from 23 to 83 years, at that average age and its median was smaller in OC patients. In this group number of patients aged before 50 and after 50 was the same, whereas in the groups 1 and 2 there were more patients younger than 50 years, and in the group 4 - more patients older than 50 years. In patients of all the groups at primary reference to oncologist tumor process stages I-III were diagnosed. According to the data of tumors morphological study it was determined that in BC patients ductal cancer and scirr were diagnosed (differentiation degree G1 and G2), in CUC patients – adenocarcinoma (G0 and G1), in OC patients – mainly serous cancer forms (G3), in CC patients – most frequently adenocarcinoma was diagnosed (G2).

Time interval before metachronous tumors diagnostics varied from two to 31 years. In contrast to synchronous tumors, the majority of metachronous tumors were diagnosed in patients after 50 years (30/75%) and only in 10/25% patients secondary tumors developed in the age less than 50 years.

Metachronous tumors had different histology, at that some patients with CUC, BC, OC had two tumors. Secondary tumors were diagnosed at I-III stage of neoplastic process. Taking into consideration that OC, BC and CUC (primary tumors) are hormone-mediated, it may be suggested that metachronous tumors development in these patients is associated with hyperestrogenia that is involved in the mechanisms of hormone-mediated tumors pathogenesis. The later represented 36 (75%) tumors from total number of 47, among them CUC represented 19 (39.6%), BC – 7 (14.6%), OC - 10 (20.8%).

Table 4. Results of clinical, morphological and clinical-genealogical studies in patients with primary multiple metachronous cancer (n=40)

	Patients' groups and primary tumors			
Patient's groups	**I group**	**II group**	**III group**	**IV group**
Tumors	**BC**	**CUC**	**OC**	**CC**

Patients' number	12	10	6	12
Patients' age (range), average age/ age median (Me)	33 – 83 49.2 / 45	33-78 48.3 / 46	23-67 43 / 40.5	26 – 68 50 / 52
Patients' number under 50 years / older than 50 years	8 / 4	6 /4	3 /3	3 / 9
Stage	1a – 3c	1a – 3b	1a-3c	1 – 3c
Pathomorphological diagnosis	Ductal infiltrative cancer, scirrhus	Adenocarcinoma	Serous papillary cancer (3), serous adenocarecinoma (2), dysgerminoma (1)	Adenocarcinoma (8), mucinous (2), carcinoid (1), basal cell cancer (1)
Metachronous tumors				
Time interval before metachronous tumors diagnostics	2 – 22 years	4 – 27 years	3 – 31 years	3 – 19 years
Metachronous tumors	CUC (6), OC (6), bilateral BC (1), sarcoma (1), cancer of thyroid gland (1)	CC (6), BC (3), OC (2), SC (1), skin cancer (1), Hodgkin lymphoma (1)	CUC (3), BC(3), SC(1)	CUC (10), OC (2)
Number of tumors / number of patient in the group	15 / 12	14 / 10	7 / 6	12 / 12

Patients' number under 50 years / older than 50 years	4 / 8	2 / 8	3 / 3	1 / 11
Stage	1a – 3c	I – 2b	Ia-2b	1a – 2a
Differentiation degree	CUC (G0-G2) OC(G2-G3) BC bilateral (G2) Sarcoma (G3) Cancer of thyroid gland (G1)	CC (G1-G2) BC (G1-G3) OC (G2) SC (G3) Skin cancer (G1) Hodgkin lymphoma (HodLym)	CUC (G0-G1) BC (G1- G2) SC(G1)	CUC (G0-3) OC (G1- G2)
Pathomorphological diagnosis	Adenocarcinoma, ductal infiltrative cancer, serous adenocarcinoma, leiomyosarcoma	Adenocarcinoma, ductal infiltrative cancer, basal cell cancer, squamous cell cancer, chronic lympholeucosis	Adenocarcinoma, medullar cancer, ductal cancer	Adenocarcinoma, serous papillary, granulose cell cancer
Total malignant tumors number in family trees / in relatives of first genetic relationship	24 / 14*	18 / 9	8 / 5	26 / 12 *

Note:* primary multiple cancer in proband's mother; CC – colorectal cancer, SC- stomach cancer.

Rather important from the viewpoint of hereditary factors role in tumors development and family cancer syndrome were clinical-genealogical data, according to which in 40 pedigries of patients with metachronous malignant neoplasias were determined 74 relatives of different relationship degree, who

suffered from cancer of different genesis. Among 74 relatives malignant tumors were in 38 (51.3%) relatives of the first degree of relationship (16 mothers and 14 fathers, 3 daughters, 2 brothers and 3 sisters**)** and in 36 (48.7%) relatives of the second degree of relationship (17 aunts and 4 uncles, 12 grandmothers and 3 grandfathers). In general, according to clinical-genealogical data in 6 (12.8%) of 47 families cancer family syndrome was determined with aggregation of tumors of ovaries, breast, corpus uteri and gastro-intestinal tract and also of tumors of another genesis, in 3 patients hereditary cancer was determined (OC, BC, UBC). According to literature [19], family cancer history in patients with UBC and OC is determined in more patients (28 %).

Five patients from total number of examined parsons had several metachronous tumors (Table 3). They were patients with BC (2), CUC (2) and OC (1). It is meaningful that in all observations, except N42, it is possible, according to clinical-genealogical data, to determine Lynch syndrome II.

Table 5. Individual characteristics of patients with several metachronous tumors

N of case and diagnosis	**Patient's age, stage and morphological peculiarities of tumor process**				**Clinical-genealogical data**
	Primary tumor	**First metachronous tumor**	**Second metachronous tumor**	**Third metachronous tumor**	
N27	33 years	40 years	61 years	-	BC in mother, BC and OC in aunts, CC in uncle
Clinical diagnosis	BC, st.2a	TC, st.1	OC st. 3c		
Pathomorphologic diagnosis	Ductal infiltrative cancer	Papillary	Endometrioid adenocarcinoma		
N36	36 years	57 years	57.5 years	-	BC and CerC in mother,
Clinical diagnosis	BC st. 2	OC st. 3c	BC st. 2b		

Pathomorphologic diagnosis	Solid cancer	Serous adenocarcinoma	Bilateral ductal infiltrative cancer		BC in sister, LC in father
N16	23 years	50 years	54 years		CC in mother, LC in uncle
Clinical diagnosis	OC st. 1c	CUC st.1b	BC st. 1		
Pathomorphologic diagnosis	Serous cystadenocarcinoma	Adenocarcinoma	Ductal infiltrative cancer		
N19	47 years	59 years	69 years	-	
Clinical diagnosis	CUC st. 3	CC st. 1	HodLym st.3		
Pathomorphologic diagnosis	Adenocarcinoma	Basal cell cancer	Chronic lympholeu-cosis		SC in two brothers
N42	50 years	75 years	77 years	77 years	Kidney cancer in grandfather
Clinical diagnosis	CUC st. 2a	CC st. 2	Cancer of skin,st. I	Lymphoma st.4a	
Pathomorphologic diagnosis	Papillary adenocarcinoma	Basal cell cancer	Squamous cell cancer	Hodgkin lymphoma	

Note: TC – thyroid cancer

How it is evident from the presented study data in many patients with primary hormone-dependent tumor synchronous or metachronous tumor is also hormone-dependent, which may indicate commonality of their pathomorphosis. It is worth to mention that in malignant growth development, besides hormonal disorders and genetic predisposition, other endo- and exogenous factors are also implied that may affect FRSO causing pathological alterations to them. According to literature [24, 25], not only deteriorations of hormonal homeostasis, but also metabolic changes presence in organism lead to polyneoplasias development. Keeping that in mind active search for alterations in target organs of hormonal influence, especially in cancer patients, is absolutely necessary stage after treatment of BC, OC, CUC patients to assess their risk of secondary tumors development.

Indeed, the biggest interest is evoked by patients with pedigries, where mothers and fathers of probands with synchronous and metachronous tumors had

malignant tumors that is impotrant for hereditary cancer forms determination. How it is seen from the Fig. 2 the most common pathology in probands' fathers was gastro-intestinal cancer and lung cancer, in mothers - gastro-intestinal cancer and BC.

According to obtained results we are unable to determine factors that have influenced malignant growth in members of given families; although we can state that morphological and clinical diagnoses and PMMs clinical-genealogical study data suggest hereditary character of the disease – 6% of patients have hereditary CUC, OC, BC (Figs. 3, 4), 12.8% of patients have cancer family syndrome (Fig. 5).

According to molecular-biological and clinical cancer research hereditary factor of tumor disease is based on studies of genetic predisposition to cancer development that consist in exploration of predisposing genes to FRSO cancer development [20,21,27,29]. Molecular studies were tevealed mutations in tumor growth suppressor genes - *185delAG, 5382insC*, *2080delA*, *4154delA* (gene *BRCA1*) and *6174delT* (gene *BRCA2*), and also mutations in DNA reparation genes - *hMLH1* and *hMLH2*. Also was found tendency to develop primary multiple breast or ovary lesions in persons with abnormal methylation in *RASSF1A, RARβ2* [4]. Therefore, the necessity of further molecular-genetic examinations of patients with FRSO cancer, especially those that have primary multiple tumors and their relatives for presence of mutations in genes-suppressors of tumor growth *BRCA1/2* or single nucleotide polymorphism (SNP) does not raise doubts. Such studies should promote clarification of genetic alterations and their association with polyneoplasias development.

To identify mutations in genes *BRCA1* (*185delAG* and *5382insC*) and *BRCA2* (*6174delT*) that are the most widespread in Slavic population we conducted molecular-genetic study of tumors excised from patients with PMMs of FRSO. According to molecular-genetic study results, in the tumors of 8 (18.2%) of 44 patients were determined mutations in the gene *BRCA1- 5382 insC* in 4 patients with PMMs of FRSO, in the gene *BRCA2 - 6472 delT* - in 4 patients with PMMs

of FRSO + gastro-intestinal cancer. At the other hand mutation in the gene *BRCA1 - 185 delAC* was not detected in any case (Table 6). During comparison of mutational alterations in tumor cells with clinical peculiarities of tumor process in PMMs patients it was noted that in presence of mutations in the genes *BRCA1* (*5382insC*) and *BRCA2* (*6472delT*) synchronous formation of malignant FRSO tumors was observed in 5 of 8 patients.

Table 6. Genes BRCA1/2 mutations frequency and characteristics in the patients with PMMs of FRSO (n=44)

Mutations in the genes	***BRCA1 (185 del AC)***	***BRCA1 (5382 ins C)***	***BRCA2 (6174 del T)***
Mutations number and characteristics (in parentheses tumors association in proband and number of patients)	0	4 (BC+OC - 3) (BC+CUC - 1)	4 (CUC+OC - 1) (BC+OC - 1) (OC+SC - 1) (CUC+CC -1)
Total number of patients with mutations, n /%	8 (18.2%)		
Total number of examined patients, n /%	44 (100%)		

Based on the above, if given family has patients with cancer tumors of FRSO and genetic alterations in proband relatives the absolutely necessary measure is persons arranging into genetic risk groups of cancer development in such families, and elaboration of cancer monitoring tactics. For the benefit of persons' monitoring from families with PMMs patients there are studies [7] demonstrating that in CUC patients relative risk of BC was 13.6 at the first year of observation, 5.3 - at the fifth year of observation, 3.9 – at the tenth year, 3.0 – at the fifteenth year. BC patients also have high relative risk of CUC development, especially for the first year of observation – 9.0, for fifths – tenth – 2.0-2.2, for 15-

th – 3.6. It was established that synchronous BC, associated with mutations in the genes BRCA1/2, is determined in 50% of patients, and in case of primary multiple pathology (BC and OC) in 100% of patients germinal mutations in DNA reparations genes are detected, This allows to distinguish hereditary oncological syndrome comprising BC and/or OC [10]. These examples demonstrate pathogenetic commonality and predisposition for synchronous and metachronous BC, CUC, OC development and critical need to provide clinical-genealogic analysis of families with frequency determination of malignant tumors aggregation in the family, especially in relatives of the first genetic relationship. Such approach is an important step towards determination of PMMs development risk in probands, and also for tumor pathology screening, especially BC, CUC, OC**.**

Therefore our results indicate actuality and perspective of further study of such underexplored problem as PMMs of FRSO. Important significance in future have not only clinical, morphological and clinical-genealogic studies, but also molecular-genetic studies that determine biological manifestations of tumor processes.

Conclusions

1. PMMs (synchronous and metachronous) of FRSO are characterized by individual variability in terms of neoplastic growth manifestations. In 75% of patients with PMMs of FRSO metachronous tumors developed after the age of 50 years.

2. Among metachronous tumors in patients with PMMs of FRSO most frequently diagnosed CUC (39.6%), OC (20.8%), BC (14.6%) that may indicate common mechanisms of hormonal pathogenesis.

3. The majority (89.4%) of synchronous and metachronous tumors had epithelial pathogenesis, their histological structure corresponded to adenocarcinomas of different differentiation degree and squamous cell cancer.

4. According to clinical-genealogical data of probands (PMMs patients) malignant tumors of different genesis were observed in 51.3% relatives of I genetic relationship, and in 48.7% relatives of II genetic relationship In 12.8% of PMMs patients Lynch syndrome was determined with aggregation of tumors of ovaries, breast, uterus and gastro-intestinal tract; in 6% of patients – hereditary cancer of ovary, uterus or breast.

5. In 18.2% patients with synchronous PMMs were determined mutations in *BRCA1* and *BRCA2* genes that suggested the role of genetic factors in the development of primary-multiple tumors of FRSO.

6.Clinical-genealogical analysis of pedigree should be considered as integral part of complex examination of families that have patients with BC, CUC, OC for determination of metachronous tumors development risk in probands, and also as a measure for development of genetic monitoring principles in probands' families and cancer prevention in theirs families members.

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