The role of molecular-genetic counseling in detection of benign and malignant pathology of female reproductive system organs

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The objective: **introducing the questionnaire method to identify families with aggregation of tumor pathology in the population of Cherkassy region (in patients with benign and malignant diseases of the female reproductive system (OZHRS) with a history of cancer family histo; ry), an in;depth clinical examination of women of those families, and bringing the feasibility of health genetic counseling for the diagnosis of tumor pathology and the formation of high;risk groups of precancer and cancer OZHRS.**
***Patients and methods*. Medical and genetic counseling 1103 (100%) patients and the introduction of their questionnaire method during the reception at the gynecologist;oncologist 343 (31,1%) of patients with cancer of the female reproductive system were conducted (ROZHRS) and a gynecologist – 760 (86,9%) in healthy women who applied for the purpose of baseline medical examination, to identify families with aggregation of tumor pathology.**
***Results*. Analysis of clinical and genealogical data for women from such families found that the association of cancer in these families cor; responds to a cancer family syndrome (Lynch II syndrome) or family cancer. A comprehensive clinical examination of probands revealed malignant and benign pathology of breast, cervical and endometrial, ovarian and digestive tract.**
***Conclusion*. The results are the testimony of the effectiveness of the introduction of profiles, questionnaires in medical practice for clinical and genealogical analysis and evaluation of family onkoanamneza to identify a group of inherited risk ROZHRS, as well as for the timely diagnosis of precancerous and tumor pathology processes in family members s aggregation of malignant tumors.**
Key words: *cancer of female reproductive system organs, hereditary cancer syndrome, medical-generic counseling of family trees.*

Cancer of female reproductive system organs (FRSO) is one of the most actual oncology problems that is stipulated by increase of its morbidity in females of different ages both in Ukraine and abroad. Such thesis relates entirely to cancer of female reproductive system organs which in Ukraine, according to the data of the National Cancer register, has no tendency to decrease. In the structure of female pathology cancer of breast, uterine body, and ovary occupy the first rank places.

The foregoing demonstrate that the problem of cancer of female reproductive system organs is actual not only medical, but also social problem that requires urgent solution of such important issue as reduction of morbidity and mortality of patients with cancer of female reproductive system organs. One way to decrease mortality and delayed diagnosis of such patients – is optimization of tumor process diagnostics at early stages and, therefore, increase of share of patients with initial stages of malignant process at which curative treatment is possible, and also development of methodological approaches to screening of the said pathology. Positive solution of these issues will be possible due to application of state-of-art scientific results of fundamental character, based on achievements of molecular biology in the area of natural history of malignant growth.

According to modern ideas, tumor development – is a result of complex and multistage process of accumulation of structural and functional effects of oncogens and suppressor genes. It is known that gene mutations facilitate development of mutant cell that does not mean equivalence to tumor cell development; also it is worth mentioning that mutant cell is more inclined to new mutational alterations. Different kind of mutations can emerge both in germinal and in somatic cells. In case of germinal mutations – they are transferred by hereditary principle, and every cell of the body that inherited germinal mutation will have genetic alterations that reflect instability of new organism's genome. Namely germinal mutations underlie the development of hereditary and familial cancer forms.

Basing on positions of clinical oncogenetics, the term «hereditary» in relation to cancer development means not the transfer of tumor nodule, but only predisposition to its development. In other words, predisposition to tumor development – is genetically determined organism's condition, caused by certain functional state of organism's systems (immune, hormonal, nervous) at which the risk of tumor growth is significantly larger than in other person under the action of the same factors of endogenous or exogenous origin.

Molecular-genetic studies of the recent years that were done in Ukraine, Russia, Sweden and other countries substantiated the role of hereditary factors in predisposition to cancer development. These studies determined that cancer related to multi-factor pathology; in predisposition to cancer the important role played genetic factors (predisposition of organism to the development of hereditary pathology) and environmental factors (radiation, exposure to sunlight, occupational hazards, lifestyle, and others). Highly-penetrant germinal mutations in *BRCA1* and *BRCA2* genes are associated with high risk of cancer development [1–3].

These genes belong to genes-suppressors of tumor growth that are involved in reparation of DNA damage and maintenance of cells' genetic stability. Therefore their mutations that cause disorder of cellular genetic homeostasis are critical, and their accumulation promotes alterations in cells' function. Therefore today the problem of genetic disposition to FRSO cancer is one of the most actual [7, 8].

With molecular-genetic studies it was determined that cancer – is a disease of genome, and the majority of human malignant tumors had multi-factor origin, in other words, in their development the complex of factors, among which there are genetic and environmental factors, played its role. The latter factors that increase the risk of malignant cancers development are occupational hazards, ionizing radiation, cancerogens, air pollution, ultraviolet irradiation, infectious factors, smoking, alcohol,

Tabl. 1

The questionnaire, developed by the authors of the study
QUESTIONNAIRE (filled by patient)

Full name
Date of birth "___" _____19___ Age – (how many complete years)
Place of residence (region, district, city, village) completely –
Category (if Chernobyl certificate is present) –
– When have you been last time at prophylactic examination at gynecologist? (date)
– When have you been last time at dispensary examination at oncologist (oncosurgen, oncogynecologist)? (date)
Data about family members
Did your father suffered from cancer ..... in what age..... diagnosis.....
Did you mother suffered from cancer ..... in what age..... diagnosis.....
How many full sisters you have.....
How many of them suffered from cancer.....in what age..... diagnosis.....
How many full brothers you have .....
How many of them suffered from cancer ..... in what age..... diagnosis.....
How many children you have: sons..... daughters.....
How many sons suffered from cancer .....in what age.....diagnosis.....
How many daughters suffered from cancer .....in what age..... diagnosis.....
Did your relatives on the maternal line suffered from cancer?
Grandmother ..... in what age.....diagnosis.....
Grandfather ..... in what age.....diagnosis .....
How many aunts you have (had).....from them suffered from cancer .....in what age.....diagnosis .....
How many uncles you have (had).....from them suffered from cancer ..... in what age.....diagnosis
Did your relatives on the paternal line suffered from cancer?
Grandmother ..... in what age.....diagnosis.....
Grandfather ..... in what age.....diagnosis .....
How many aunts you have (had).....from them suffered from cancer .....in what age.....diagnosis .....
How many uncles you have (had).....from them suffered from cancer ..... in what age.....diagnosis
Date of questionnaire filing ..... Patient's signature .....

nutritional habits, stresses, and others. Although the effect of these hazardous factors on human organism depends on genetic stability/instability of organism that, according to the results of recent studies, underlie the development on oncologic diseases and hereditary predisposition to cancer development [5, 7].

Clinical studies demonstrate that, in spite of significant advances in improving treatment methods for oncologic patients and application of novel cytostatic preparations, their mortality does not have significant tendency to decrease because of tumor processes diagnostics at late stages of their development. Therefore, from the position of strategy of fight against cancer nowadays the priority is given both to prevention and early diagnostics of pre-cancer and cancer, but solution of these issues is complicated by the absence of organized system and scientifically-based programs. However, one of the effective measures that could facilitate early cancer and pre-cancer diagnostics is the development of screening (*screening* – selection) programs. The aim of such programs – is to detect disease at early stages of development when the symptoms are absent and curative treatment is possible.

In our opinion, advances of clinical oncogenetics, where both theoretical bases of genetic and molecular biology of tumor growth, and practical experience of oncologists concerning hereditary and familial forms of cancer of breast, ovaries, uterus, colon and other tumors are integrated, can be included into selective screening programs [5, 6].

Genome instability, mutations in the genes of germinal cells that are transferred from generation to generation, additional mutations in somatic cells of organism can facilitate development of malignant tumors in several members of the same family, at that hereditary cancer forms, Lynch syndromes of types I and II, or other oncogenetic syndromes develop [1–3].

Major clinical criteria that suggest hereditary nature of oncologic disease are the following: increased frequency of cancer of the same genesis in several generations (ovarian or breast cancer) or cancers of different genesis (ovarian and breast cancer, cancer of uterine body and colon, and others), tumor process manifestation at a young age, paired organs involvement, multiplicity of tumors that develop either synchronously or metachronously. To determine hereditary forms of malignant tumors in families in case when above mentioned features are present classical method of medical genetics is used – clinical-genealogical examination with family trees composition, determination of the type of pathology transfer from generation to generation, and assessment of risk of its possible development in cancer patient's descendants with genetic-mathematic analysis.

From the standpoint of presented above, exploration of family morbidity – is a key to understanding of hereditary factors role in multi-factor diseases etiology, and examination of members of family with tumor pathology accumulation – is a clinical model of determination of genetic predisposition to cancer development and risk of its occurrence. Therefore, in our opinion, introduction of oncogenetic counseling of oncologic patients into clinical practice will facilitate determination of families with tumor pathology accumulation in family trees for further extended clinical and genetic examination of members of such families to detect pre-clinical cancer forms or primary-multiple pathology.

Tabl. 2

The results of medical genetic counseling of patients in 1103

Patients that sought medical advice for prophylactic examination	Patients with FRSO cancer (343/100%)			
Practically healthy (760/100%)	Uterine body cancer, 143 (41,7%)	Ovarian cancer – 55 (16,0%)	Breast cancer – 99 (28,9%)	Primary-multiple tumors (PMT) – 46 (13,4%)
Family cancer syndrome (FCS), determined in 9,6% of surveyed females	FCS – in 23,1%	FCS – in 29,1%	FCS – in 40,4%	FCS – in 53,6%

Totally medical-genetic counseling and clinical-genealogical analysis of 1103 questionnaires was provided

The importance of oncogenetic counseling is confirmed by NSGC (National Society of Genetic Counselors) that officially defined genetic counseling of patients as a process to aid medical, psychological and family adaptation of oncologic patients and to better understand genetic contribution into disease development. Major stages of such counseling are the following. At first – it is examination of cancer family history and determination of number of patients with cancer of different localization in several family generations, comparison of diagnoses, determination of hereditary component. One more important stage – diagnostics of proband's relatives' disposition, including his/her descendants, to the development of malignant pathology, associated with indicated genes mutations, in ovaries, breast and other organs. Obtained complex information, in its turn, will serve as substantiated basis for formation of genetic risk groups of cancer development in family, implementation of prophylactic measures, monitoring of health condition of family members and diagnostics of pre-cancer processes or cancer at pre-clinical stage. The complex of presented preventive measures corresponds to the most actual issues of predictive and preventive medicine, and actuality of such a concept is based on developed state-of-art protocols and models for genetic examination of oncologic patients.

Since 2007 till nowadays we provide complex examinations concerning the role of genetic factors in predisposition to FRSO cancer development, fundamental substantiation of malignant tumors development in healthy members of families with tumor pathology aggregation.

The objective: to introduce questionnaire method for detection of families with tumor pathology aggregation among the population of Cherkassy region (in patients with benign and malignant FRSO pathology with cancer positive family history), to provide extended clinical examination of females from such families and to prove reasonability of medical-genetic counseling for diagnostics of tumor pathology and formation of increased risk groups in development of pre-cancer and cancer of FRSO.

PATIENTS AND METHODS

For this purpose we used questionnaire method of clinical-genealogical data acquisition. All females of Cherkassy region that sought gynecologist's attention for prophylactic examination in the medical center «Andromeda-plus Ltd» (Cherkassy) or consulted gynecologist-oncologist in CE "Cherkassy Regional Oncologic Dispensary" of CRC were proposed to fill themselves the questionnaire that we developed (Tabl. 1), from which we learned about presence or absence of relatives, suffered from cancer, in the families.

Note: For the oncologic patients:

The tumor was self-detected or it was detected during prophylactic examination? (underlie needed)

– How many years (months) you are ill? .....

– How long after the first complains you sought doctor's attention?.....

– What was doctor's specialization whom you visited for complains – oncologist, gynecologist, therapist, surgeon or other doctor?..... (underline or write down)

Questionnaires data were analyzed, and according to the results of clinical-genealogical analysis of patients' family trees, medical-genetic counseling was provided for 1103/100% patients, which were 343/31.1% FRSO patients during their visit to gynecologist-oncologist n oncogynecological center of CE «Cherkassy Regional Oncologic Dispensary» of CRC, and also 760/86.9% patients of medical center «Andromeda-plus» during routine inspection by doctor – gynecologist whom these patients visited for prophylactic examination and actually they did not have any complains.

Analysis of the questionnaires allowed selecting families in which there were relatives of I-II degree of kindred, suffering from cancer. In these cases medical-genetic counseling of the patients (probands) with family trees composition was provided. Analysis of family trees comprised estimation of malignant tumors frequency in generations, family relationship of these sick relatives to proband, number of healthy family members and family members with cancer that further allowed determining hereditary type of the disease. On condition of cancer patients in the family from 760 practically healthy females the group of 73/9.6% was selected from 760/100% females; in this former group family cancer syndrome (FCS) was determined. These patients were referred to extended clinical examination, comprising breast ultrasound (US) or mammography, US of abdominal cavity organs and thyroid gland, roentgenography of thoracic organs, immunoenzyme examination of CA125 concentration, blood tests, including biochemical, and urine analysis. In all these females cervical canal smears and aspirates from uterine cavity were examined, in some of these patients morphological examination of uterine wall scrapings and cervical biopsy specimens was provided when it was indicated. Extract from medical records, certificates from other medical institutions, and consultants' conclusions were also applied. All laboratory analysis were conducted after females counseling by oncologist and oncogenetics, after counseling family situation considering frequency of cases of oncologic disease in families was assessed.

And among 343/100% FRSO patients medical-genetic counseling was provided for 143/41.7% patients with uterine body cancer (UBC), 99/28.9% patients with breast cancer (BC), 55/16.0% patients with ovarian cancer (OC), and 46/13.4% patients with synchronous primary-multiple tumors (PMT) of female reproductive system organs. Clinical-genealogical analysis of family trees determined in these patients family cancer syndrome (FCS) in 23.1% patients with UBC, in 29.1% patients with OC, in 40.4% patients with BC, and in 53.6% patients with synchronous PMT of FRSO, indicating the significant contribution of hereditary factor to the development of these FRSO forms (Tabl. 2).

Basing on the analysis of genealogical data and results of oncologic pathology determination in probands among 73 family trees those family trees that had family cancer syndrome (32) and hereditary cancer (7) were identified. Among the latter hereditary forms of breast cancer (3 family trees), breast and ovarian cancer (1), ovarian cancer (1) and gastro-intestinal tract (2) were determined. In 3 probands from these families breast cancer was diagnosed, in 4 persons diffuse fibroadenomatosis of breast, large ovarian cysts, uterine body adenomatosis, and polycystic ovarian disease were diagnosed.

All females with determined oncologic and pre-cancer pathology received appropriate treatment according to the stan-

dards, adopted in Ukraine. Together with their relatives these females, including those after received treatment, were assigned to the groups of potential genetic risk of oncologic pathology development, considering the possibility of development of primary-multiple oncologic pathology in members of families with family cancer syndrome. In addition, for every female the individual schedule of dispensary observation was composed with fixed data of repeated observations and examinations.

Obtained results demonstrate reasonability of implementation and medical-genetic counseling of females from families with aggregation of tumor pathology. The received data may serve as a basis for establishing a register of families with family cancer syndrome and hereditary cancer in female population of Cherkassy region.

Therefore, with questionnaire method, following medical-genetic counseling of females from families having relatives of I-II degree of kindred, suffering from cancer, and extended examinations of these females both malignant and benign pathological processes in different organs and also their association were determined. It demonstrated that clinical-genealogical examination should become primary and essential stage of complex patients' examination at first referral of patients to specialized oncologic medical institutions.

The value and necessity of this approach was discussed in 2010 at 60-th Annual Meeting of American Society of Human Genetics, where the importance of clinical-genealogical data for the assessment of the risk of tumor pathology development was emphasized. It was stated that the risk of oncologic pathology development depended on patients' family health (family health history-based risk assessment – FHRA) and results of personal genomic screening (personal genomic screening – PGS-test). As an example, the results of application of FRHA-test were presented, in consequence of which the patients with high risk of breast cancer development were determined. Although it was stated that the largest weight any individual family history got in complex with genetic patients' examination (genomic screening), family history remained «gold standard» in assessment of personal risk of disease and it could be considered as «secret weapon» in integration of personalized data and genetic knowledge into clinical practice.

Oncogenetic patients' counseling – is an important approach both to early diagnostics, and to cancer prevention, in this approach several steps can be specified: 1 – screening and creation of registers of patients with hereditary nature of the disease; 2 – genetic examination of patients: 3 – establishment of register of patients with possible development of genetically determined cancer forms. In this regard genetic examination of probands (patients with cancer) and their relatives aims to identify mutations of genes, involved in development of hereditary cancer forms, namely *BRCA1* and *BRCA2* genes. These genes are genes-suppressors of tumor growth, although mutations of both their alleles are associated with development of cancer of breast, ovary, uterine body, and prostate in members of families with tumor pathology aggregation.

Genetic examination of patients' relatives is necessary for determination of the risk of tumor pathology development or for its diagnostics at preclinical stage when disease symptoms are absent. Analogous examination of newly diagnosed cancer patients (breast and ovarian cancer) allows determining hereditary cancer forms (including *BRCA1/2*–associated forms) that differ in biological characteristics from sporadic cancer forms. It allows providing personalized approach both to early cancer and pre-cancer diagnostics, and adequate treatment of cancer patients that in future will help to avoid serious complications of therapy and to improve quality of live. Introduction of the results of new theoretic findings about genetic causality of cancer and the role of hereditary factors in its development into practical oncology will allow making cancer prevention more effective that in general will facilitate reduction of cancer incidence in female population of Ukraine.

Conclusions

1. Analysis of data of questionnaires that were obtained from 760 females demonstrated that in 73 (9,6%) family trees there were 1–5 relatives of I–III degree of kindred, suffering from cancer, at that the share of family trees with 2–5 cancer patients was 91,8%. In the families of examined probands malignant tumors association corresponded to family cancer syndrome (Lynch syndrome II) or hereditary cancer.

2. Clinical-genealogical examination of 73 females with aggregation of tumor pathology of Lynch II type and their extended clinical examination allowed to detect malignant tumors of different genesis in 35,6% of cases, in 64,4% of cases benign tumors, pre-cancer and inflammatory processes were determined. Moreover, among malignant tumors that were diagnosed in probands FRSO cancer prevailed, among the pathology of benign character the most frequently diagnosed were pathological processes of uterine body and cervix, breast, ovary. In the same patients association of several pathological processes in different organs was observed.

3. Clinical-genealogical analysis of family trees determined family cancer syndrome (FCS) in 23,1% patients with UBC, in 29,1% – with OC, in 40,4% – with BC, in 53,6% – with synchronous PMT of FRSO that indicated significant contribution of hereditary factor in the development of said forms of FRSO cancer.

4. The obtained results indicate efficiency and reasonability of application of questionnaires in medical practice as a simple screening method for determination of families with tumor pathology aggregation and for further extended examination of such families' members for pre-clinical or early diagnostics of tumor pathology and pre-cancer processes.

Роль медико-генетического консультирования в выявлении доброкачественной и злокачественной патологии органов женской репродуктивной системы

О.В. Палийчук

Цель исследования: внедрение анкетного метода для выявления семей с агрегацией опухолевой патологии среди населения Черкасского региона (у больных с доброкачественной и злокачественной патологией органов женской репродуктивной системы (ОЖРС) с отягощенным раком семейным анамнезом), проведение углубленного клинического обследования женщин из таких семей и доведение целесообразности медико-генетического консультирования для диагностики опухолевой патологии и формирования групп повышенного риска развития предрака и рака ОЖРС.

Материалы и методы. Было проведено медико-генетическое консультирование 1103 (100%) пациенток и внедрение у них анкетного метода во время приема у гинеколога-онколога 343 (31,1%) больных с раком органов женской репродуктивной системы (РОЖРС) и у врача-гинеколога – 760 (86,9%) практически здоровых женщин, которые обратились с целью профосмотра, для выявления семей с агрегацией опухолевой патологии.

Результаты. Анализ клинико-генеалогических данных у женщин из таких семей установил, что ассоциация злокачественных опухолей в этих семьях соответствует семейному раковому синдрому (синдром Линча II) или семейному раку. Комплексное клиническое обследование пробандов выявило злокачественную и доброкачественную патологию молочных желез, шейки и тела матки, яичников и пищеварительного тракта.

Заключение. Полученные результаты свидетельствуют об эффективности внедрения анкет-опросников в медицинскую практику для проведения клинико-генеалогического анализа и оценки семейного онкоанамнеза с целью выявления групп наследственного риска возникновения РОЖРС, а также для своевременной диагностики опухолевой патологии и предраковых процессов у членов семей с агрегацией злокачественных опухолей.

Ключевые слова: *рак органов женской репродуктивной системы, наследственный раковый синдром, медико-генетическое консультирование, анкетный метод, родословные.*

Роль медико-генетичного консультування у виявленні доброякісної та злоякісної патології органів жіночої репродуктивної системи

О.В. Палійчук

Мета дослідження: впровадження анкетного методу для виявлення родин з агрегацією пухлинної патології серед населення Черкаського регіону (у хворих на доброякісну та злоякісну патологію органів жіночої репродуктивної системи (ОЖРС) з обтяженим на рак сімейним анамнезом), проведення поглибленого клінічного обстеження жінок з таких родин та доведення доцільності медико-генетичного консультування для діагностики пухлинної патології та формування груп підвищеного ризику щодо розвитку передраку і раку ОЖРС.

Матеріали та методи. Було проведено медико-генетичне консультування 1103 (100%) пацієнток та впровадження у них анкетного методу під час прийому у гінеколога-онколога 343 (31,1%) хворих на рак органів жіночої репродуктивної системи (РОЖРС) та у лікаря-гінеколога – 760 (68,9%) практично здорових жінок, які звернулись з метою профогляду, для виявлення родин з агрегацією пухлинної патології.

Результати. Аналіз клініко-генеалогічних даних у жінок з таких родин встановив, що асоціація злоякісних пухлин у цих сім'ях відповідає сімейному раковому синдрому (синдром Лінча II) або спадковому раку. Комплексне клінічне обстеження пробандів виявило злоякісну та доброякісну патологію молочних залоз, шийки і тіла матки, яєчників та травного тракту.

Заключення. Одержані результати свідчать про доцільність упровадження анкет-опитувальників у медичну практику для проведення клініко-генеалогічного аналізу та оцінювання сімейного онкоанамнезу з метою виявлення груп спадкового ризику щодо виникнення РОЖРС, а також для вчасної діагностики пухлинної патології та передракових процесів у членів родин з агрегацією злоякісних пухлин.

Ключові слова: *рак органів жіночої репродуктивної системи, спадковий раковий синдром, медико-генетичне консультування, анкетний метод, родоводи.*

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Статья поступила в редакцию 07.04.2016