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Clinical aspects of medical-genetic counseling and genetic testing of twins, including those from families with family cancer syndrome

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The cases of benign and malignant tumors development in family trees of cancer patients and in twin sisters are described. The results of complex examination and medical genetic counseling of examined persons are discussed. Polymorph variants T-397C, A-351G of the gene ERS1 (CC and GG genotypes), genotype AG of the gene Cyp2D6 were determined that suggest the requirement for medical-genetic counseling and molecular-genetic testing for determination of gene ERS1 polymorphism in females from families with family cancer history, in particular, in twins.

Key words: *family tree, proband, twins, hereditary predisposition, gene ERS1 polymorphisms.*

Increased incidences of breast cancer, cancer of ovaries, uterine body and other organs brings on the cutting edge novel methods of early cancer diagnostics and prevention that can be based on achievements of molecular oncology. Therefore, the current stage of development of cancer care is characterized by improvement of traditional ways of prophylaxis and diagnostics of malignant tumors of different genesis. In recent years medical-genetic counseling and genetic testing of patients with malignant processes became increasingly widespread.

Genetic counseling of patients (NSGC – National Society of Genetic Counselors) was officially recognized as a process of assistance to oncologic patients for their medical, psychological and family adaptation, and also for better understanding of genetic contribution to disease development. First step in such assistance is exploration of cancer family history by clinical-genealogical examination of proband (person whose family tree is analyzed) and determination of number of patients, suffering from cancer of different localization, in several generations of family. Second step – is testing of proband and her family members for mutation in genes-suppressors of tumor growth *BRCA1* and *BRCA2*, and also for polymorphism of estrogen receptor gene *ERS1*. Determination of such genetic alterations – is an evidence for existence of genetic component of tumor disease. This is supported by results of molecular-genetic examination of proband and her relatives, as literature data suggest that mutation, appearing in germinal cells, can be passed on from generation to generation by autosomal dominant type. Tumors of different genesis (breast cancer, ovarian cancer, colorectal cancer) may result from this process. In other words, germinal mutations in genes-suppressors of tumor growth *BRCA1* and *BRCA2* predict possible development of familial or hereditary forms of breast cancer and ovarian cancer in families [1–4].

Similar investigations are performed in other countries for prevention of individual risk of colorectal cancer development in the frames of manifestation of Lynch II syndrome II and other tumors [5–8]. However, unified system or program to compare clinical manifestations of cancer and genetic testing results for prevention strategy for most common cancer forms has not been developed yet. It is particularly true for childhood malignant tumors which make up to 10% among all diagnosed tumors.

Aim of the work: to determine potential genetic risk of oncologic pathology development in probands' families and twin sisters, basing on results of clinical-genetic examination and genetic analysis of estrogen receptor gene *ESR1*.

Over the last 3 years clinical, clinical-genealogical and molecular-genetic examinations were conducted in patients with benign and malignant tumors of female reproductive system organs (FRSO) that were receiving treatment in CE «Cherkassy Regional Oncologic Dispensary" of Cherkassy Regional Council. Molecular-genetic methods include identification of *5382insC* and *185delAG* mutations in the gene *BRCA-1*, 6174delT in the gene *BRCA2*, polymorphous variants *T-397C, A-351G* of the gene *ERS1* and of the gene *Cyp2D6* in peripheral blood and surgical material with multiplex polymerase chain reaction (PCR). Molecular-genetic studies were conducted in SE «Reference centre for molecular diagnostics of the Ministry of Public Health of Ukraine». We consider that clinical cases of probands with tumor pathology of FRSO and their twin sisters deserve special attention taking into account results of genetic testing of females from families with cancer positive family history.

Clinical case № 43. Proband – female patient D.L.V., born 1971, resident of Cherkassy, Ukrainian, profession – manager. Obstetric anamnesis is not burdened, pregnancies were absent, menarche at the age of 14, menstruations for 4–5 days in 30 days, menstrual cycle is regular. At the age of 41 she underwent surgery of electrocauterizing colonization of cervix uteri for cervical Ca in situ. In the same year she was diagnosed with diffuse fibroadenomatosis of breast, for this condition she received conservative medical therapy. The patient also received treatment for seasonal aggravations of uterine appendages inflammation and periodical development of functional follicular ovarian cysts with moderately expressed pain syndrome and without menstrual cycle disorder.

Pathohistological conclusions: cervical tumor – non-keratinizing squamous cell cancer, histological grade G1. Cervical cancer developed on the background of infection with highly oncogenic types of human papilloma virus (HPV), for this she received post-operative course of anti-virus therapy and immunotherapy until complete elimination of virus pathogen.

Clinical-genealogical analysis of family free (fig. 1) determined the following: in I generation lung cancer in father (68 years) and breast cancer in paternal aunt (64 years). Twin sister of proband died at the age of 21 of acute leukemia. Basing on obtained results of clinical-genealogical analysis of family tree family cancer syndrom was determined. Results of molecular-genetic study of proband: polymorphous variants*T-397C, A-351G* of the gene *ERS1*

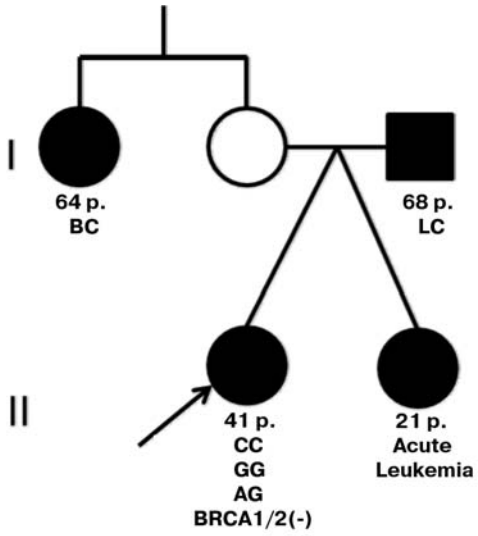

Fig. 1. Family tree of proband D., 41 year (observation № 43).
Family cancer syndrome. Proband has cervical Ca in situ. In I generation of her family tree LC in father and BC in maternal aunt (2 patients) at the age of 68 and 64 years, respectively. Twin sister of proband died at the age of 21 of acute leukemia. Results of molecular-genetic study of proband: polymorphous variants T-397C, A-351G of the gene ERS1 (genotypes CC and GG),of the gene Cyp2D6 (AG),genes BRCA1/2 (-).

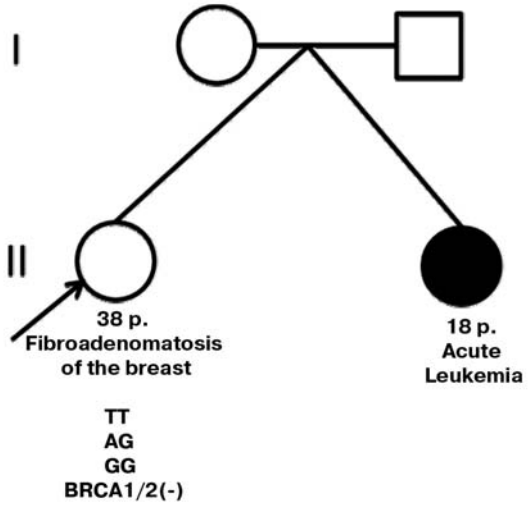

Fig. 2. Family tree of proband K., 38 years (observation №72).
Proband has breast fibroadenomatosis. Her twin sister died at the age of 18 of acute leukemia Results of molecular-genetic study of proband: polymorphous variants T-397C, A-351G of the gene ERS1 (genotypes TT and AG), of the gene Cyp2D6 (GG),genes BRCA1/2 (-)

(genotypes *CC* and *GG*), of the gene *Cyp2D6 (AG),* Mutations in the genes *BRCA1* та *BRCA2* were not detected.

Legend: BC – breast cancer, LC – lung cancer, CC – cervical cancer.

Clinical case № 72. Proband - female patient K.T.V., born in 1974**,** resident of Cherkassy region, Ukrainian, profession – teacher. Obstetric anamnesis: deliveries – 1 (at the age of 24), abortions – 0, miscarriages – 0, menarche at the age of 14, menstruations for 4–5 days in 30 days, menstrual cycle is regular, lactation – up to 12 months. Intrauterine device – was absent. At the age of 38 breast fibroadenomatosis was diagnosed (prolactin levels in serum and blood), for this condition she received conservative medical therapy (herbal medicinal products, sedating medication) for moderate premenstrual syndrome along with dynamic ultrasound breast examination every 6 months. The patient also received treatment for seasonal aggravations of uterine appendages inflammation. Her twin sister died at the age of 18 of acute leukemia (fig. 2).

Results of molecular-genetic study of proband: polymorphous variants *T-397C, A-351G* of the gene *ERS1* (genotypes *TT* and *AG*), of the gene *Cyp2D6 (GG)* were determined. Mutations in the genes *BRCA1* are *BRCA2* were not detected.

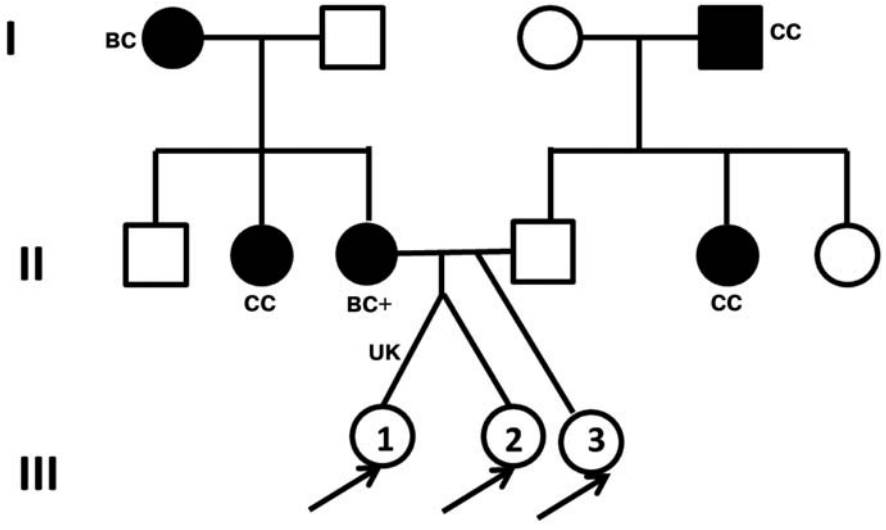

Fig. 3. Family tree of 3 probands – sisters (observation No. 80, 81, 82).
Family cancer syndrome. Matrilineally – breast cancer (BC), gastric cancer (GC) and polyneoplasia – breast cancer (BC) and uterine body cancer (UBC); patrilineally – two cases of colon cancer (CC). Probands 1 and 2 – are twins P. and V., 40 years. Clinical diagnosis – uterine body adenomyosis and diffuse breast fibroadenomatosis in both twins. Polymorphous variants T-397C, A-351G of the gene ESR1 (genotypes CC and GGгенотипі) of the gene Cyp2D6 (AG) in probands 1 and 2, genes BRCA1/2 (-). Proband 3 – P., 30 years. Clinical diagnosis – ovarian polycystosis. Polymorphous variants T-397C, A-351G of the gene ESR1 (genotypes TC and AG) and of the gene Cyp2D6 (AA), genes BRCA1/2 (-).

Clinical case № 80, 81, 82. Probands – three sisters, two of them are twin sisters. Probands 1 and 2 – are twins P. and V., born 1972, at the moment of examination their age was 40 years, proband 3 – P., born 1982, at the moment of examination her age was 30 years. All females are residents of Cherkassy, Ukrainians, all of them have higher education (profession – managers). Obstetric anamnesis: in probands 1 and 2 is similar: deliveries 1 (at the age of 23 in proband 1 and at the age of 24 in proband 2), abortions – 0, miscarriages – 0, menarche from the age of 14, menstruations for 5–6 days in 30 days, menstrual cycle is regular, lactation by 6 months. Intrauterine device – was absent. In proband 3 obstetric anamnesis is not complicated, deliveries were absent, menstrual cycle is regular, menarche from the age of 12 for 4–5 days in 28 days. At the age of 40 both twin sisters were diagnosed with uterine body adenomyosis and diffuse breast fibroadenomatosis (confirmed by ultrasound examination, and at the age of 30 proband 3 was diagnosed with ovarian polycystosis at ultrasound examination. Twin sisters received symptomatic conservative medical therapy, and third sister was prescribed with 2-phase oral contraceptive for contraception, and she received recommendations concerning pre-conceptional preparation in case of aimed pregnancy.

Clinical-genealogical analysis of family (fig. 3) tree of these probands determined family cancer syndrome of the family tree: matrilineally – breast cancer in grandmother and gastric cancer in aunt, and polyneoplasia – breast cancer and uterine body cancer in mother; patrilineally – two cases of colon cancer – in aunt and grandfather.

In twin sisters with molecular-genetic testing the following molecular alterations of genotype were detected: in probands 1 and 2 – polymorphous variants *T-397C, A-351G* of the gene *ESR1* (genotypes *CC* and *GG*) of the gene *Cyp2D6 (AG)*, and in proband 3 – polymorphous variants *T-397C, A-351G* of the gene *ESR1* (genotypes *TC* and *AG*) and of the gene *Cyp2D6 (AA)*. Mutations in the genes *BRCA1* and *BRCA2* were absent in all sisters.

CONCLUSION

Presented results of complex examination of twin sisters indicate the presence of genetic alterations in them on the basis of relatives with cancer. From this results it can be stated that there is a need for both clinical-genealogical and molecular-genetic examination of females from families with aggregation of tumor pathology and establishment of register of families with family cancer syndrome where in proband's relatives malignant processes in female reproductive system organs and gastro-intestinal tract are observed. The females with genetic mutation in the gene *ER1* or in the genes-suppressors *BRCA1* and *BRCA2* should be aware of the clinical significance of identified genetic alterations and possible risks of tumor pathology development both in themselves and in their relatives. The females with mutations in these genes also require enrollment into groups of prevention and treatment of chronic diseases and precancerous processes, in particular, of female reproductive system organs. Described clinical cases of malignant processes in twin sisters are of major interest for doctors in various fields, in particular, for genetics, oncologists, obstetricians, gynecologists, and pediatricians.

Клинические аспекты медико-генетического консультирования и генетического тестирования близнецов, в том числе из семей с семейным раковым синдромом

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В статье описаны случаи в родословных возникновения доброкачественных и злокачественных опухолей больных раком и у сестер-близнецов. Оценены результаты комплексного обследования и медико-генетического консультирования обследованных. Установлены полиморфные варианты T-397C, A-351C по гену ERS1 (CC- и GG-генотипы), генотип AG по гену Cyp2S6, что свидетельствует о необходимости проведения медико-генетического консультирования и молекулярно-генетического тестирования на полиморфизм гена ERS1 женщин из семей с отягощенным по раку анамнезом, в том числе близнецов.

Ключевые слова: *родословная, пробанд, близнецы, наследственная предрасположенность, полиморфизмы гена ERS1.*

Клінічні аспекти медико-генетичного консультування і генетичного тестування близнюків, у тому числі з родин із сімейним раковим синдромом

О.В. Палійчук, Л.З. Поліщук, З.І. Россоха

У статті описані випадки у родоводах виникнення доброякісних та злоякісних пухлин хворих на рак та у сестер-близнюків. Оцінено результати комплексного обстеження та медико-генетичного консультування обстежених осіб. Установлено поліморфні варіанти T-397C, A-351G за геном ERS1 (CC- та GG-генотипи), генотип AG за геном Cyp2D6, що свідчить про необхідність проведення медико-генетичного консультування та молекулярно-генетичного тестування на поліморфізми гена ERS1 жінок із родин з обтяженим на рак анамнезом, у тому числі близнюків.

Ключові слова: *родовід, пробанд, близнюки, спадкова схильність, поліморфізми гена ERS1.*

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