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RISK ASSESSMENT OF CANCER OF THE FEMALE REPRODUCTIVE SYSTEM

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***Aim*: To create an information resource concerning multifactorial oncological diseases of the female reproductive system. *Materials and Methods:* A comprehensive search of the literature in the PubMed and Ukrainian scientific sources published from 1995 to 2014 and the results of researches performed in R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine. Development environment of information resource "Multifactorial oncological disease" was Borland Delphi. *Results*: The information content of web page concerning cancers of the female reproductive system was posted in the information resource "Multifactorial oncological disease". The assessment algorithm of genetic contribution to cancers of the female reproductive system and recurrent risk of cancer development in families have been described. These algorithms can be used in assessment of contribution of genetic and environmental factors in the development of malignant tumors.**
***Key Words*: cancers of the female reproductive system, information resource, genetic contribution, recurrent risk.**

Despite progress in anticancer campaign in Ukraine, this problem is still relevant for public health. According to the data of epidemiological studies of National Cancer Institute of Ukraine, overall incidence of malignant neoplasms (MN) in Ukraine has increased in 2011 compared with 2010 on 2.7% among female population and on 1.6% among men. When characterizing structure of MN morbidity in 2011, we can note that MN of breast, corpus uteri, uterine cervix, colorectal cancer and non-melanoma skin MN take rank places among women — 58.8% and the most widespread MN in men are prostate gland cancer, gastric, colorectal, lung cancer, non-melanoma skin MN — 57.8% [1].

To date, it is beyond the question that cancer problem can be solved only on conditions of development of measures of cancer disease prophylaxis, increase of level of timely diagnostics of MN and carrying out of adequate therapy. One more condition which has essential significance for improvement of treatment results is providing of patient care institutions with modern equipment and instrumentation and increase of level of vocational training of oncologists.

Subsidiary, and in series of cases, crucial significance for timely diagnostics and determination of treatment tactics have modern knowledge which can be obtained in systematized, formalized and structured forms.

However, dynamic development of computer information technologies in medical and biological spheres can both accelerate and complicate obtaining and interpretation of required information on given problem in connection with its permanent updating, representation in various formats and by different stage of detailing.

For this reason, important element of treatment-and-diagnostic process is creation of information resource as theoretical basis with system of hyperlinks on Internet resources for effective access to information and its use as basis for development of prophylaxis system and algorithms of diagnostics of cancer diseases which would include methods of assessment of hereditary and recurrent risk of MN of different genesis.

Aim of the research was to create information resource on multifactorial cancer diseases of female reproductive system which occurrence has polygenic nature.

METHODS

Systemic analysis of the problem, generalization of information, structural and functional study of subject for the application of knowledge in the context of multifactorial cancer diseases have been used. Development environment of information resource was Borland Delphi. For the functioning of system, operating platform Windows and dynamic libraries of Delphi resources have been used.

RESULTS AND DISCUSSION

Work on creation of information resource "Multifactorial cancer diseases" has been divided in the stages by degree of topicality and sequence of their performance which included analysis of information (generalization and systematization of theoretical knowledge of foreign and national scientific literature as well as results of own studies of stuff of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, choice of conception of information presentation), development of structure, programming and entry of the information.

Information on cancer diseases of female reproductive system, namely risk factors, genetic features

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Abbreviations used: BC – breast cancer; CFRS – cancers of the female reproductive system; CUC – cancer of the uterine cervix; EC – endometrial cancer; HPV – human papilloma virus; MN – malignant neoplasms; OC – ovarian cancer.

of MN, prognostic markers and prophylactic measures concerning occurrence of cancer diseases has been analyzed.

On the basis of analysis, a structure has been developed which included the following parts for each localization: classification of malignant tumors by TNM (2009), FIGO (2009) and WHO (2014) and their phenotype parameters, algorithm of diagnostics and prognostic markers.

According to the structured information concerning endo- and exogenous factors of predisposition to MN, it has been determined that most of cancers of the female reproductive system (CFRS) are multifactorial diseases. It means that occurrence of such cancer diseases is connected both with genetic factors and with impact of various bad environmental factors which cause the disorders of systems of regulation of differentiation and proliferation of cells. At that, multifactorial inheritance and part of hereditary factor varies for individuals of different sex by age, for tumors of different genesis and geographic regions [2–5]. When analyzing inheritance of breast cancer (BC), ovarian cancer (OC) and cancer of the uterine cervix (CUC) within the framework of multifactorial model, genetic determinant in development of these diseases constitutes 55.7 ± 2.4%; 66.8 ± 6.3% and 2.9 ± 2.6%, correspondingly. These data show that, on the one hand, there is different impact of genetic and environmental factors on development of the disease, and, on the other hand, they are heterogeneous [3–5].

Some other researchers have determined certain relation between malignant process and individual predisposition to occurrence of tumor. For instance, we shall focus on some important results of study, namely occurrence of 85–90% of BC cases is connected with epigenetic changes in *BRCA1* gene [6, 7], in 15–43% of cases — with amplification of *HER2/neu (ErbB-2)* gene [8], and in 20% of cases — with spontaneous mutations of *TP53* gene and in 12.0% — with mutations of *MMR* family genes [9]. It should be mentioned that 5–10% of cases of OC develops on the background of germinal mutations of series of genes-suppressors (*BRCA1/BRCA2, TP53, CHEK2, PTCH, VHL, NBS1)*, genes of *FANC* and *MMR* family which are responsible for reparation of unpaired bases of DNA within the limits of series of family cancer syndromes. It has been showed that risk of OC in women with Lynch syndrome II constitutes 9–12% [10–13]. At the same time, decrease of expression of *BRCA1* gene (in result of epigenetic changes or alternative splicing) has been noted in 65–82% of sporadic cases of OC [14, 15]. Besides mentioned above, in 50–66% of malignant ovarian neoplasms, inactivation (mutations or epigenetic changes) of gene-suppressor *TP53* [16–18] is being determined, in 28.0–40.0% — decrease of expression of *PTEN* gene [19], amplification of genes *Her2/neu (ErbB-2)* — in 16–32%, *EGFR (c-erbB-1)* — in 9–17% of cases and in 15% of cases — mutation changes of *KRAS* gene [20, 21].

Our studies have determined significant decrease of expression of receptors of estrogens and progesterone in highly proliferative and low differentiated serous OC [22].

Molecular aspects of development of endometrial malignant tumors are broadly covered in literature. For instance, occurrence of endometrioid adenocarcinoma in 83% of cases is associated with inactivation of *PTEN* gene (mutations or deletions), mutations of genes *PIK3CA* (26–36%), *KRAS* (10–30%), — β-catenin*/CTNNB1* (14–44%) and *TP53* (10–20%), inactivation of $p16^{INK4a}$ (10%), amplification of *Her2/neu* (10–30%) and loss of E-cadherin (10–20% of cases) [23].

In contrast to previously mentioned, in serous malignant endometrial tumors, genetic changes in listed above genes are to be found with other frequency. Mostly in such tumors are detected mutations in gene-suppressor *TP53* (90%), loss of E-cadherin is determined in 60–90% of cases, inactivation of $p16^{INK4a}$ in 40–45% of tumors, amplification of *Her2/neu* in 18–80% of observations. Along with it, changes in functioning of *PTEN* gene is being observed only in 11% of cases, mutations in *PIK3CA* — 5%, *KRAS* and *CTNNB1* are detected in 5–10% of tumors [23]. It has been showed that increased risk of endometrial cancer (EC) and early debut of colorectal cancer are associated with family history of women both without mutation of genes of *MMR* family and with mutations in these genes within the limits of Lynch syndrome, have general hereditary and environmental factors [24, 25]. Despite contribution of genetic component to occurrence of CUC is quite insignificant (2.9%), but in tumor cells of uterine cervix spontaneous mutations, deletions or epigenetic changes of genes-suppressors *ST3, FHIT,* proto-oncogenes *EGFR, FGFR3* and *c-MYC* and oncogene *c-FOS* are registered [5, 26–30]. Along with this, it has been determined to date that leading role in development of CUC belongs to human papilloma virus (HPV) [31–33], oncogenes *EGFR, FGFR3* та *c-MYC* and oncogene *c-FOS* [5, 26–30].

Some researchers state that infection agents, as HPVs, are risk factors of occurrence not only of CUC, but also have certain pathogenic role in development of EC, OC and BC [34–39]. It can be confirmed not only by results of our previous studies which have showed that in the condition of infection by virus, tumor cells of ovary are characterized by low expression of proteins — tumor suppressors p53 and pRb [40–42] that is typical for HPV-associated neoplasms.

It is known that "trigger" of pathological process can be both genetic and environmental factors associated with high risk of MN. Vector of development of MN is determined depending on individual genetic constitution of organism. For instance, along with impact of biological factors influencing the occurrence of cancer diseases, potential ecological risk factors which are connected with environment in concrete geographical region and physical and chemical agents cannot be excluded [43–46].

At the same time, question concerning assessment of MN risk still remains open, namely question concerning contribution of hereditary and environmental factors to development of MN, exactly CFRS, criteria of individual prognosis of this pathology are also not determined.

In part "Prognostic markers", rates of unfavorable clinical course of disease, measures of prophylaxis according to the each localization of CFRS are given.

Part "Algorithm of diagnostics" included information according with subsections: clinical criteria; laboratory indexes; risk factors. The latter includes developed by us algorithm of assessment of risk of disease, to be exact cancer, which is located in information field of the resource "Multifactorial cancer diseases". Assessments of genetic predisposition to cancer pathology (Fig. 1) and recurrent risk of disease in progenies (Fig. 2) are carried out by clinical and genealogical data obtained at individual inquiry of persons or patients with histologically verified diagnosis.

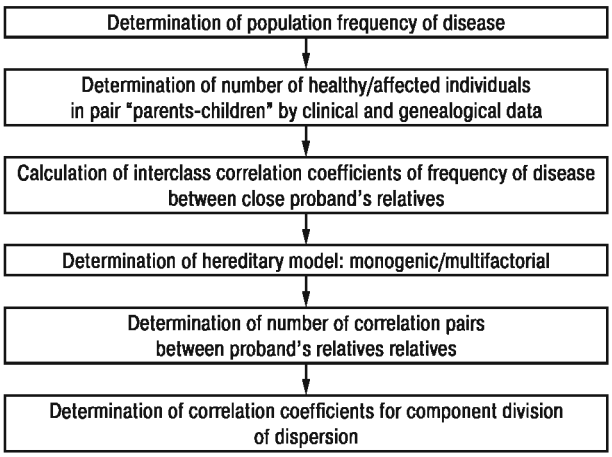

Fig. 1. Algorithm of assessment of contribution of genetic and environmental components to predisposition to disease

Algorithm 1 includes:

- determination of population frequency in calculated time period by data on population size and population morbidity in corresponding geographical region;
- determination of frequency of occurrence of disease and number of affected relatives by principles of analysis of individual's pedigree (proband's);
- determination of relations between proband's relatives (genetic-correlation analysis) for assessment of genetic predisposition to disease;
- calculation of correlation coefficients between relatives before manifestation of disease within the limits of monogenic model (alternative distribution of predisposition to disease) and multifactorial model (quasi-continuous distribution);
- carrying out of genetic analysis of multifactorial signs (component analysis);
- assessment of correlative contribution of genetic and environmental components to occurrence of disease taking into account coefficient of affinity using procedure of component division of phenotype dispersion for determination of role of hereditary factor by proband's pedigrees in determination of occurrence of disease.

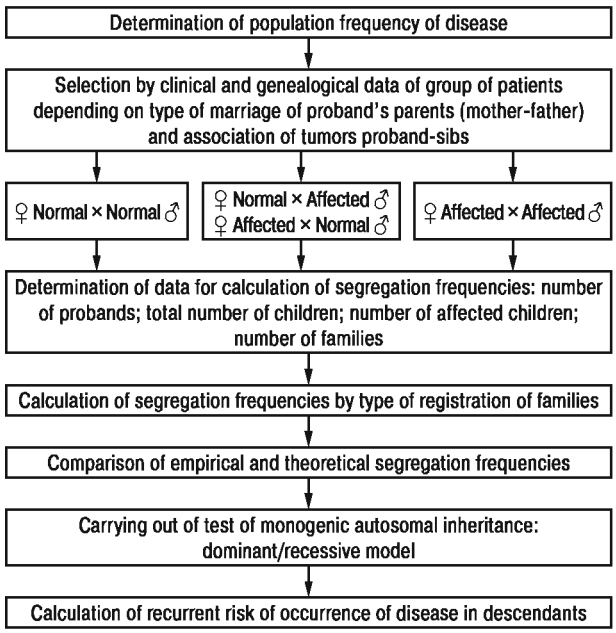

Fig. 2. Algorithm of assessment of recurrent risk of disease in progenies

Algorithm 2 includes:

- determination of population frequency in calculated period of time by data on population size and population morbidity in corresponding geographical region;
- formation of groups according to clinical and genealogical information depending on type of marriage of proband's parents (normal or affected);
- determination of quantitative rates of normal-affected persons in family;
- carrying out of segregation analysis: distribution of disease in series of generations according to monogenic (autosomal-dominant and autosomal-recessive type of inheritance) and polygenic (multifactorial) model with differentiating approach considering family history of cancer according to genealogic data;
- comparison between empirical segregation frequencies and theoretically expected frequencies for prognosticated type of inheritance;
- calculation of recurrent risk of disease in progenies based on segregation frequencies.

Practical use of algorithms 1 and 2 at clinical and genealogical examination of 142 patients with EC living in Kyiv region allowed obtaining the following results.

1. It was determined that the population frequency of EC in women of Kyiv region equaled to 0.26%.

2. Coefficient of genetic correlation between first degree relatives of proband with EC was 0.53 that corresponds to the quasi-continuous distribution of predisposition to CFRS.

3. Contribution of genetic factors in the development of CFRS constituted 53.2 ± 5.6%, environmental factors — 46.8 ± 5.6%.

4. Quantitative indexes of association EC — CFRS were determined in sisters of proband considering the type of parents' marriage: both parents are healthy — N×N (Normal-Normal) and one or both parents of proband are cancer-affected — N×A

(Normal-Affected) and A×A (Affected-Affected) and segregation frequency of cancer development in families was calculated. If proband has healthy parents — segregation frequency constitutes 1.89 ± 0.009, cancer affected parents — 4.38 ± 0.034.

5. The model of inheritance on the basis of testing of monogenic autosomal inheritance by Student's criterion was determined. The obtained indexes exceeded critical values at level of significance t(5%) = 1.96, indicating that dominant and recessive models cannot be fully accepted.

6. The probability of CFRS development was calculated for probands' descendants depending on the health of parents: for the first child of healthy parents, cancer risk constitutes 0.3%, and for the second child — 1.6%. In cancer affected parents, probability of cancer for the first child equals 13.5, for the second — 19.3%.

Thus, information resource "Multifactorial cancer diseases" provides effective access to the information concerning cancer diseases of polygenic nature with the aim to use them in scientific and practical activity in the field of cancer genetics.

The main technical parameters of information resource are that it is directed to the work both in autonomous (network) and local version without limitation of number of users. In program, the mechanism of direct editing of data in web-fields without use of additional editors of HTML-documents has been implemented. Organization of simple interface is adapted for users who are not specialists in the domain of information technologies.

Represented algorithm of assessment of contribution of genetic and environmental components to predisposition to occurrence of diseases, including cancer, as well as recurrent risk of cancer in progenies, can be used as base for development and realization of preventive measures in medical and genetic consulting.

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