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BREAST CANCER AND HEREDITARY TUMOR SYNDROMES: A MODERN PARADIGM

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Abstract

About 5–10% of malignant neoplasms (MN) are hereditary. Carriers of mutations associated with hereditary tumor syndromes (HTS) are at high risk of developing tumors in childhood and young age and synchronous and metachronous multiple tumors. At the same time, this group of diseases remains mainly an oncological problem, and clinical decisions are made only when MNs are detected in carriers of pathogenic mutations. Individual recommendations for cancer screening, treatment, and prevention should be developed for carriers of mutations associated with HTS to prevent an adverse outcome of the disease. It is essential to identify patients at risk by doctors of all specialties for further referral to medical and genetic counseling with molecular genetic testing (in case of indications). The problems of standardization of enrollment criteria for genetic tests, further tactics of prevention, screening, and treatment of many hereditary oncological diseases remain unsolved. About 5–10% of malignant neoplasms (MN) are hereditary. Carriers of mutations associated with hereditary tumor syndromes (HTS) are at high risk of developing tumors in childhood and young age and synchronous and metachronous multiple tumors. At the same time, this group of diseases remains mainly an oncological problem, and clinical decisions are made only when MNs are detected in carriers of pathogenic mutations. Individual recommendations for cancer screening, treatment, and prevention should be developed for carriers of mutations associated with HTS to prevent an adverse outcome of the disease. It is essential to identify patients at risk by doctors of all specialties for further referral to medical and genetic counseling with molecular genetic testing (in case of indications). The problems of standardization of enrollment criteria for genetic tests, further tactics of prevention, screening, and treatment of many hereditary oncological diseases remain unsolved on screening measures, diagnosis, and treatment of HTS underline the need to review the existing and develop new algorithms for medical support of patients with HTS.

Key words

hereditary cancer, hereditary mutations, hereditary breast cancer syndrome, DNA repair genes.

Genetic predisposition to cancer has been noted since the late 19th century, when cases of repeated occurrence of cancer in individual families were described. Since the discovery of the first genes associated with hereditary cancer in the 1990s, their number has steadily increased and the clinical phenotypes associated with them have been increasingly understood, with the gradual discovery of more pathogenic mutations, as well as the development of high-throughput sequencing technologies (Next Generation Sequencing, NGS) all Multigene testing with simultaneous analysis of many genes is gaining greater practical importance. This reduces the time to results when three or more genes need to be analyzed. Since testing involves the analysis of genes with different penetrance, in some cases even low or unknown, with its wider use in clinical practice, there is an intensive accumulation of information about new pathogenic variants, as well as clarification of the penetrance of already known ones. In addition, the use of the NGS method makes it possible to compare certain combinations of mutations with the phenotype observed in NOS, to identify new correlations of mutations and an increased risk of cancer (for example, an increased likelihood of breast cancer in

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the presence of a mutation in the PMS2 gene). At the same time, the likelihood of detecting mutations of unknown clinical significance increases. This, and the lack of clinical guidelines for identifying variants with intermediate or low penetrance, makes data interpretation difficult. Even more information and at the same time uncertainty is provided by the use of whole exome and whole genome.

In this way, data on new pathogenic variants can be obtained, but determining their penetrance requires studying large groups of patients over a long period of time. Given the high cost of the analysis, this approach is rarely used in clinical practice, but has potential for wider use, including due to a gradual reduction in price. The use of whole exome and whole genome sequencing is advisable if other genetic methods do not identify the cause of NOS. Regardless of the result obtained, genetic testing may be useful in the following cases:

• if the result is positive, the patient will be able to manage risks (for example, lifestyle changes, regular testing or preventive surgery may increase chances of a successful outcome);

• if cancer has already been diagnosed, the results of genetic testing may be useful in choosing treatment options;

• if the result is informatively negative, the patient will know that he has not inherited a pathogenic gene variant, which is important for psychological peace of mind;

• if the result is positive, family members will also have the opportunity to learn about their risks of SDE.

However, negative consequences of genetic testing are also possible. Primarily, there is psychological stress when a pathogenic variant is detected or when an uninformative result is obtained (for example, when a VUS is detected). If the test result is negative, you may feel guilty towards relatives who have been diagnosed with genetic disorders. It should also be noted that the cost of genetic testing, although constantly decreasing, remains high. Therefore, it is very important that the patient gives informed consent to genetic testing, understanding both its possible benefits and its limitations. Approximately one in twelve women will develop breast cancer during her lifetime. The main etiopathogenetic factors of hereditary breast and ovarian cancer (BC and OC) are changes in the BRCA1 and BRCA2 genes. About 5% of breast cancer cases are caused by a mutation in one of two genes. Other genes are also known, mutations in which are associated with hereditary forms of breast cancer and ovarian cancer. In carriers of mutations in the BRCA1 or BRCA2 genes, the risk of developing breast cancer and ovarian cancer during life is on average 80% and 20–40%, respectively. Male carriers of the mutation usually do not get the disease, but have an increased risk of breast cancer and may pass the mutation to their offspring. Men who carry a BRCA1 mutation have a greater risk of prostate cancer, while those with a BRCA2 mutation have a higher risk of breast cancer. Identification of the most common hereditary defects in the BRCA1 and BRCA2 genes has become a routine component of the examination of patients with breast and ovarian carcinomas. The purpose of such activities is not only to search for relatively healthy relatives who are carriers of BRCA1/2 mutations, but also to modify the drug treatment regimen for an existing cancer. Despite the intensive dynamics of the formation and changes in the criteria for searching for mutations in the BRCA1 and BRCA2 genes in international and Russian practice, the main ones can be identified:

1. Breast cancer was detected before the age of 50 years;

2. bilateral breast cancer;

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3. Breast cancer and ovarian cancer in the same patient or in the same family;

4. two or more types of cancer that may be associated with BRCA1/2 mutations in the same family member;

5. cases of breast cancer in men;

6. Ethnicity: Ashkenazi Jews.

A pathogenic mutation in the BRCA1/BRCA2 genes can be detected in approximately 50% of families with suspected hereditary forms of breast cancer and ovarian cancer. If the presence of breast cancer and/or ovarian cancer in a family is accompanied by the detection of a mutation, relatives at risk are recommended to undergo regular screening for early diagnosis of the disease. It should be taken into account that a negative test result for frequent mutations does not exclude the presence of pathogenic changes in the gene. PALB2 and breast cancer. Given the close relationship of PALB2 with BRCA and the process of homologous recombination, the researchers concluded that the new gene may also be associated with hereditary cancer syndromes. In 2007, scientists from the UK analyzed PALB2 in 923 people with a family history of breast cancer (BC) and found mutations in 10 of them (1.1%). Scientists estimate that the presence of the mutation was associated with approximately twice the risk of developing breast cancer in women [8]. Subsequently, these data were confirmed by researchers from different countries, although the incidence, spectrum of mutations, and assessment of the risk of breast cancer varied. Table 1 presents data from some of the largest studies of mutations in the PALB2 gene in breast cancer. In Finland, the founder mutation was isolated in 2007, first from a sample of 113 people (3 with the c.1592delT mutation) with a family history of cancer, and then from an unselected sample of 1,918 Finnish residents (18 cases of the c.1592delT mutation). The authors also noted an earlier age of onset of cancer in carriers of the PALB2 mutation (52.9 years), which is generally higher than in carriers of mutations in the BRCA1 (46 years), BRCA2 (48 years), but less than the average age of women with Breast cancer without mutation (57.8 years) [10]. An American study in 2011 involved 1,144 people, of whom 33 had a defective PALB2 gene. At the same time, the authors separately identified a group of 172 Ashkenazi Jews, suggesting that they may likely have their own “founder” mutations (similar to the BRCA genes). But among this group there was not a single carrier of a mutation in the PALB2 gene. When analyzing the data, scientists concluded that the relative risk increased by 2.3 times by age 55 and by 3.4 times by age 85. In addition, it was interesting that all 7 carriers of the c.509-510delGA mutation reported German ancestry (later it turned out that they had a common ancestor who immigrated to the United States in the 19th century).

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