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CLINICAL IMPORTANCE OF DEFINITION OF SINGLE NUCLEOTIC POLYMORPHISMS IN PATIENTS WITH BREAST CANCER (LITERATURE REVIEW)

Abstract. Purpose of the review: The study of literature data relating to the replacement of nucleotides in DNA with the risk of development, course and prognosis of breast cancer.

Materials and methods. A literature review was conducted in electronic databases included in PubMed/Medline, The Cochrane Library. The depth of search was 10 years.

Results. The data on the role of single nucleotide polymorphisms in the development, course, prognosis and response to treatment for breast cancer in individual populations was studied. The research results show that the replacement of nucleotides in DNA underlies the differences in susceptibility to the development of diseases, the effectiveness of the action of medicines.

Conclusion. The determination of single nucleotide polymorphisms can reveal a hereditary predisposition to various multifactorial diseases (including cancer), and to predict individual sensitivity to pharmacological medicines. This can help physicians choose the most effective treatment for breast cancer patients.

Keywords: breast cancer, single nucleotide polymorphism, prognosis of the course, risk of development.

Introduction. Breast cancer affects up to 12% of women worldwide. According to statistics, in the United States, in 2015, nearly 3 million cases of breast cancer were registered [1]. Risk factors for breast cancer include lifestyle, other pathological conditions, and genetic predisposition [2]. Epidemiological studies show that women with a family history of breast cancer have a higher risk of developing than those who do not have it [3].

Numerous recent studies have reported on the association between single nucleotide polymorphisms (SNP) in genes and the risk of developing breast cancer. Determining the interactions of genetic factors and environmental risk factors has the potential to understand the processes leading to the development of the disease, identify women for whom these risk factors are most relevant, and improve the accuracy of epidemiological risk models.

SNP is a variation of the DNA sequence that occurs when one nucleotide (A, T, C, or G) in the genome is different from the normally expected nucleotide. These SNPs are known to be at the core of the differences in our susceptibility to developing diseases. The definition of SNP is technically not difficult and is carried out only once, which makes them relevant in quality of use as biomarkers. The number of SNPs in the human genome is about 10 million. Their changes can lead to impaired expression and regulation of genes and the appearance of proteins with altered functional properties. The corresponding germinogenic mutations alter the structure of the enzymes metabolizing medicines and transporting them, which affect the efficiency of medicine use. Knowledge of these mutations provides a rationale for individualized treatment [4, 5].

In this regard, much attention is paid to the role of SNPs in the development and progression of breast cancer, as well as their role in diagnosing and predicting the course of the disease.

The increasing interest of the role of SNP in the development and progression of breast cancer is confirmed by the number of studies and publications in the study of SNP in patients with breast cancer, but there are no clear recommendations on the application of these results.

Materials and methods. A literature review was conducted in electronic databases included in PubMed/Medline, The Cochrane Library. The depth of search was 10 years. The following search terms were used for the search: breast cancer, single nucleotide polymorphism, prognosis of the course, risk of development. Received 3192 publications on the requested terms.

Results and discussion. Environmental factors and metabolic disorders are the main causes of DNA damage [6].

Excision repair is one of the ways to restore DNA, when an exact enzymatic replacement of damaged or altered bases on one strand of the damaged two-stranded DNA molecule. Mutations that occur in related genes can lead to changes in the functions of recovery, and then significantly increase the likelihood of developing malignant tumors [7].

A number of researchers have studied the association between susceptibility to breast cancer and single SNPs in the excision repair genes. In these studies, human apurinic/apyrimidinic endonuclease (APE1), X-ray repair cross-complementing protein 1 (XRCC1), 8-oxoguanine DNA glycosylase (OGG1, also known as hOGG1) and poly (ADP-ribose) polymerase-1 (ADPAT1, also known as PARP1) were studied. Among these polymorphisms studied, the association was found between the risk of developing breast cancer and the rs25487 and rs1799782 mutations in the XRCC1 gene. A positive association between the rs25487 mutation [8–11] and the risk of breast cancer was registered in the study of one race, and was not obtained in the study of other races [12]. Most studies have shown that the rs1799782 mutation is not associated with the development of breast cancer, while in other studies, a positive correlation has been obtained [8 - 12]. Contradictory results were also presented in papers that explored populations consisting of mixed races. In 2001, Duell et al. (2001) reported that a positive association for rs25487 with breast cancer was found among African Americans, but not Caucasian Americans [13]. Vieira et al. (2015) demonstrates that the genetic background can influence the development of breast cancer and even has a reverse association [14].

A clinical study of NSABP B-31, in conjunction with the study of NCCTG N9831, established the advantage of adding trastuzumab, a monoclonal antibody targeting ERBB2/HER2 protein, to standard chemotherapy in patients with early-stage ERBB2/HER2-positive breast cancer. However, only 30 to 50% of patients use this therapy in early or adjuvant conditions [15]. Although this treatment is generally well tolerated, its cost and cardiotoxic effects and the availability of promising alternatives require research aimed at identifying patients who will not benefit from this treatment.

In the original patent of trastuzumab, two mechanisms of action are described.

First, by binding to ERBB2/HER2 on the cancer cell membrane, it prevents the dimerization of ERBB2/HER2, blocking the signaling pathway and proliferation. Secondly, it triggers the host immune system to attack and destroy the trastuzumab-associated tumor cells. This immune response, known as antibody-dependent cell-mediated cytotoxic effect (ADCC), is initiated when the FCγ receptor on natural killer cells (NK) binds to the Fc portion of trastuzumab. As a result, NK cells secrete factors, including IFN-γ, perforins and granzymes, which cause tumor cell death through the mechanism of apoptosis. A similar process, known as antibody-dependent cellular phagocytosis (ADCP).

In studies on ERBB2/HER2 breast cancer cell lines, we demonstrated potent ADCC caused by trastuzumab in vitro. Experiments in mice demonstrated a decrease in the efficacy of trastuzumab if the Fc fragment is removed from the antibody or if the mouse lacks the FCγ receptor. In addition, an increase in lymphoid cell infiltration in tumor samples was observed after treatment with trastuzumab compared with samples after neoadjuvant treatment. Taken together, these results confirm the important role of ADCC or ADCP in the mechanism of action of trastuzumab.

Additional preclinical studies have demonstrated the association of SNPs in genes encoding FCγ receptors with the strength of the immune response. Many studies have focused on the position 158 FCGR3A, which encodes valine or phenylalanine and the position 131 FCGR2A, which encodes histidine or arginine [16, 17]. In vitro ADCC assays demonstrated a large trastuzumab-mediated ADCC with the Val VGR (V)/V genotype and a tendency to associate with the histadine (H)/H genotype FCGR2A-131

[16]. Analysis of peripheral blood mononuclear cells (PBMCs), after neoadjuvant and adjuvant therapy, demonstrated more differentiated changes in gene expression in patients with V/V or H/H genotypes than in patients with phenylalanine (F)/F or arginine (R)/R genotypes, which indicates a difference in the molecular response to trastuzumab according to genotype [17]. These observations are consistent with the data that FCγRIIA-131H and FCγRIIIA-158V have a higher affinity for immunoglobulin (IgG) than proteins encoded by alternative alleles. Cells containing high affinity alleles more effectively mediate ADCC [18].

Clinical studies using therapeutic monoclonal antibodies, such as rituximab for the treatment of lymphoma and cetuximab for the treatment of colon cancer, have shown the association between the genotypes FCGR3A and FCGR2A with the effectiveness of treatment. However, clinical studies that study the association of these SNPs with the effect of trastuzumab for patients with breast cancer are not unambiguous. Tamura et al. [19] demonstrated improved response rates to trastuzumab in patients with the FCGR2A -131 H/H genotype in the neoadjuvant mode and an increase in the frequency of the objective response in the treatment of the metastatic process. Musolino A. and his colleagues [20] observed an improvement in the objective response and an increase in progression-free survival for patients with the FCGR3A -158 V/V genotype. However, when analyzing the results of the study of patients included in NCCTG-N9831 [21] and BCIRG-006 [22], no association of these loci with the efficacy of trastuzumab in the adjuvant treatment of ERBB2/HER2-positive breast cancer was found.

Fluoropyrimidines are the most common and effective chemotherapeutic agents used for the systemic treatment of various malignant tumors, including the gastrointestinal tract, breast, pancreas, head and neck cancers [23 - 25].

DPD (dihydropyrimidine dehydrogenase), encoded by the DPYD gene, is the initial and rate-limiting enzyme in the metabolic pathway of fluoropyrimidines, such as 5-Fu, capecitabine and tegafur.

The clinical significance of DPD was initially determined in connection with severe or lethal toxicity in patients receiving fluoropyrimidines who did not have or had low levels of DPD activity [26]. More than 50 DPYD polymorphisms that cause fluoropyrimidine - associated toxicity in the treatment of malignant tumors, such as breast cancer, colon carcinomas, gastroesophageal cancer and lymphoblastic leukemia have been identified [27-30].

According to a number of authors, DPYD polymorphisms can contribute to tumor progression and affect sensitivity to chemotherapy, as well as the clinical outcome of cancer patients. DPUD SNPs have been reported to lead to an increased risk of developing ovarian and gastrointestinal cancers with the DPYD genotype c.1627A> G AG / GG, resulting in low sensitivity to fluorouracil-based adjuvant therapy [29-31]. However, the prognostic value of DPYD polymorphisms in breast cancer has been little studied. Fengxia Qin et al. in their work concidered the assosiation between SNPD DPYD and the effect of therapy based on regimens containing taxanes and anthracyclines (TA) [32]. The authors found that patients with non-wild type DPYD carriers treated with the TA regimen had a longer overall survival compared with "wild type" carriers who did not receive this treatment regimen.

To date, more than 160 polymorphisms have been identified in the DPYD gene, but the number of publications on their study in Asian patients with breast cancer is very limited [33]. DPYD genetic polymorphisms can provide direct, valuable prognostic information. It is possible that for patients with breast cancer with the presence of DPYD c.1627A> G AG/GG polymorphism, chemotherapy based on fluoropyrimidines is not recommended for use.

Conclusion. The determination of SNPs can reveal a hereditary predisposition to various multifactorial diseases (including cancer), as well as predict individual sensitivity to pharmacological medicines. Considering the presence of numerous studies suggesting the possibility of developing personalized approaches in the management of breast cancer using the assessment of SNP mutations, further research is needed in individual populations. Applying this strategy can help physicians choose the most effective treatment for breast cancer patients.

Conflict of interest. The authors declare no conflict of interest.

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СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІ БАР НАУҚАСТАРДА БІР НУКЛЕОТИДТІ ПОЛИМОРФИЗМДІ АНЫҚТАУДЫҢ КЛИНИКАЛЫҚ МАҢЫЗДЫЛЫҒЫ (ӘДЕБИ ШОЛУ)

Аннотация. Мақсаты: Сүт безі обырының болжамы, ағымы, даму қаупімен ДНК-де нуклеотидтерді ауыстыруға қатысты әдебиеттегі деректерді зерделеу.

Материалдар мен әдістер. PubMed/Medline, Кокран кітапханасына кіретін электрондық дерекқорларында әдебиетке шолу жасалды. Әдебиеттерді іздеу тереңдігі 10 жыл болды.

Нәтижесі. Жеке популяцияларда сүт безі обыры кезінде емдеуге жауап беру, болжам мен ағымы, дамуындағы бір нуклеотидтік полиморфизмдердің рөлі туралы деректер зерделенді. Зерттеу нәтижелері, ДНК-дегі нуклеотидтерді ауыстыру дәрілік препараттар әсерінің тиімділігі, аурудың дамуына шалдығушылықтың түрлілігі негізінде жатқанынан хабар береді.

Қорытынды. Бір нуклеотидтік полиморфизмдер түрлі мультифакторлық ауруларға тұқым қуалаудан болатын бейімділікті (оның ішінде онкологиялық) анықтайды, сонымен бірге фармакологиялық препараттарға жеке сезімталдықты болжамдайды. Бұл дәрігерлерге сүт безі обырымен ауыратын науқастарға анағұрлым тиімді емді таңдауға көмектеседі.

Түйін сөздер: сүт безі обыры, бір нуклеотидті полиморфизм, ағымды болжау, даму қаупі.

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КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ ОПРЕДЕЛЕНИЯ ОДНОНУКЛЕОТИДНЫХ ПОЛИМОРФИЗМОВ У БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ (ОБЗОР ЛИТЕРАТУРЫ)

Аннотация. Цель обзора: Изучение данных литературы касающихся замены нуклеотидов в ДНК с риском развития, течения и прогноза рака молочной железы.

Материалы и методы. Проведен поиск литературы в электронных базах данных, вошедших в PubMed/Medline, The Cochrane Library. Глубина поиска составляла 10 лет.

Результаты. Изучены данные о роли однонуклеотидных полиморфизмов в развитии, течении, прогнозе и ответе на лечение при раке молочной железы в отдельных популяциях. Результаты исследований свидетельствуют, что замена нуклеотидов в ДНК, лежит в основе различий восприимчивости к развитию заболеваний, эффективности действия лекарственных препаратов.

Заключение. Определение однонуклеотидных полиморфизмов может выявить наследственную предрасположенность к различным мультифакторным заболеваниям (в том числе и онкологическим), а также прогнозировать индивидуальную чувствительность к фармакологическим препаратам. Это может помочь врачам, выбрать наиболее эффективное лечение для больных раком молочной железы.

Ключевые слова: рак молочной железы, однонуклеотидные полиморфизмы, прогноз течения, риск развития.

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