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BRCA1 and BRCA2 genes in breast cancer

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Abstract

Cancer is a disease characterized by uncontrolled and abnormally growing cells that develop as a result of the uncontrolled proliferation of cells in the body. With the increasing incidence of cancer day by day, cancer diagnosis and treatment methods are gaining more and more importance. Mutations in BRCA1 and BRCA2 genes are predominantly detected in the breast cancer patients. An inherited mutation in the BRCA gene becomes carried by all cells in the body. The process of carcinogenesis can begin with a "second hit" somatic mutation in the intact allele. For this reason, the identification of variants in BRCA gene mutations is important in the prevention and estimation of cancer risk and in the early diagnosis of cancer. It is recommended that people with a family history of breast cancer undergo screening for genetic risk factors. With technological developments, additional programs are being used to the models used for cancer risk detection today. In this way, it is aimed to provide effective treatment, detect cancer at an early stage, reduce cancer risks as much as possible, and ensure a long and high-quality life. In this proceeding study, we are reviewing the BRCA gene mutations and their association with breast cancer.

Introduction

Carcinogenesis is characterized by cell survival and proliferation even after genetic mutations. This genetic damage, on the other hand, can occur in the genes of the cell, and cancer can occur as a result of this uncontrolled proliferation. Regulatory genes collected in three groups:

1-Genes that can control apoptosis
2-Proto oncogenes that can ensure growth
3-Tumor suppressing genes that can inhibit growth are called.

Carcinogenesis is multi-step and occurs as a result of the accumulation of mutations in many genes within the three genes we have listed [1]. Cancer usually occurs by metastasis. Early diagnosis of cancer is life-saving, but like other diseases, it can result in death when it is delayed [2].

Examples of modifiable risk factors for breast cancer include demographic changes, physical activity, environmental factors, hormone therapy, obesity, use of oral contraceptives, smoking and alcohol use; Family history, race, early age at menopause, late menopause, age and genetic mutations can be given as examples of non-modifiable risk factors [2]. It is thought that 85% of breast cancers are caused by genetic factors. The fact that women have more breast tissue than men increase the risk of breast cancer [3]. It has been determined that 50-60% of hereditary breast cancers occur as a result of a mutation affecting one of the Breast Cancer 1(BRCA1) and Breast Cancer 2(BRCA2) genes located on the 17th chromosome [2]. The location of the BRCA mutation in the gene and the type of mutation may affect the risk of developing breast cancer. This breast cancer risk may vary depending on the median age at the time of cancer diagnosis, the nucleotide position of the mutations in patients

with germline BRCA1 and BRCA2 mutations, the functional outcome of the mutations, and the type of mutations [4]. The BRCA gene is a tumor suppressor gene, which functions as a regulatory mechanism together with its companion proteins, and as a control mechanism and repair of DNA double strand damage by homologous recombination in the cell cycle [5].

The BRCA1 gene is located on the long arm of chromosome 17 (17q21), consists of 24 exons and encodes a protein of 1863 amino acids. The BRCA1 gene is expressed in endocrine tissues and is highest in the developing neuroepithelium of the nervous system, the lifetime risk of breast cancer with a BRCA1 gene mutation is 85%, the age-related risk is 20% after the age of 40, 51% after the age of 50 and 85% after the age of 70. Epithelial neoplasms (carcinomas) are the most commonly reported histological diagnosis in patients with BRCA1 mutations. The BRCA2 gene is located on the long arm of the 13th chromosome (13q12-13), consists of 27 exons and encodes a protein of 3418 amino acids. The BRCA2 gene is expressed in normal cells, particularly in the late G1/early S phase of the cell cycle. It plays a role in double strand breaks and DNA repair. The incidence is increasing in early stage breast cancer and male breast cancer cases [6].

More than 860 mutations in the BRCA1 gene and more than 880 mutations in the BRCA2 gene have been identified. 1. Frameshift: This mutation is seen in the stages of carcinogenesis. They cause premature termination of protein translation. 2. Non-sense mutations: It occurs when a single nucleotide in a codon is replaced, and the codon, which acts as a coding, turns into a stop codon. 3. Missense mutations: Substitution of a single nucleotide in the amino acid coding stage results in the formation of a functional codon encoding a different amino acid [6].

Approximately 80-85% of the mutations are non-sense mutations or frameshift mutations that are determined to be strictly associated with the disease. Missense mutations account for the remaining 15%. Variations occur in the BRCA gene as a result of mutations. While these variations have malignant properties, pathogenic variations predispose to cancer. There are also BRCA gene mutations that cannot be detected by standard screening methods and are detected in 10% of high-risk families. It has even been stated that these mutations comprise one-third of all BRCA1 mutations [6].

Breast cancer risk assessment is of great importance in early disease diagnosis and treatment. the Gail and Claus model is frequently used to determine breast cancer risk. Today, with the increase in testing of risk factors used in these models, different programs (MYRIAD II, Tyrer-Cuzick Model/IBIS, BOIDICEA, BRCA-PRO etc.) have been developed for risk detection. Using one of these models, the risk of developing cancer or the presence of a mutation in an individual can be calculated. Today, the BRCA-PRO model is frequently used. In this model, which is based on autosomal dominant inheritance, the risks of breast cancer susceptibility 1 and 2 (BRCA1 and BRCA2) gene mutations were calculated, a three-generation family tree was drawn, and the cancer risk of the whole family was evaluated. By adding breast cancer pathological features (progesterone and estrogen receptor status, stage) into this model, the probability of detecting BRCA gene mutations has been increased. The BRCA-PRO model can provide better efficiency than models (Claus and Gail, etc.) that evaluate risks according to their subgroups (familial/genetic factors, reproductive history, demographic characteristics, etc.) [7].

Results

One in four people in the world has a lifetime risk of developing cancer. Today, more than 14 million new cancer cases are diagnosed worldwide every year. For these reasons, early diagnosis and initiation of treatment for cancer are of great importance [8]. One of the risks that cannot be changed in catching breast cancer is genetic factors. People with a family history of breast cancer are 80% more likely to have BRCA1 and BRCA2 mutations than those without. Mutations in the BRCA1 and BRCA2 genes stop the activation of the proteins, and as a result, tumor formation begins in the cell. For these reasons, it would be beneficial for individuals with a family history of cancer to have genetic screening for early breast cancer diagnosis [2].

Conclusion

Breast cancer poses a great threat especially to women with its high incidence all over the world. Thanks to raising awareness of the society, which is seen as a solution to this issue, more women today have their check-ups done at certain intervals, even though they do not have any symptoms. Curative treatment becomes possible with the diagnosis of cancer in the early stages. In this way, proposing some protective treatment methods for women in the high-risk group has increased the importance of cancer screening and identifying the patients in this group [9].

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