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Screening and Early Diagnosis of Breast Cancer

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Abstract

Breast cancer is the most common type of cancer in women and can be successfully diagnosed at an early stage. With the increase in environmental factors and stress in everyday life, it is expected that by 2030, the number of annually diagnosed cancer cases will increase significantly, which will lead to an increase in the number of new cases by 75% compared to the data of 2008. This is a serious problem, as cancer complicates people's lives from a psychological, social and economic point of view. In the fight against cancer, the development of early diagnosis and prevention methods represents the greatest value. Early diagnosis methods play an important role in detecting breast cancer

and are an important component of preventive medical care, especially at the level of primary care.

The main goal of early detection of breast cancer is to prolong people's lives, reduce morbidity and ensure quality of life. The development and use of screening methods, such as mammography, clinical examination of the mammary glands and self-examination, help to detect cancer at an early stage, which allows you to start treatment at an early stage and improves the prognosis of the disease. In essence, our goal of early detection of breast cancer is to prolong human life, as well as to reduce morbidity and ensure quality of life.

Keywords: Breast Cancer, Early Diagnosis, Oncological Screening

1. Introduction

Breast cancer is the most common malignant neoplasm in women (it accounts for approximately 25% of all oncological female diseases). Breast cancer is the most common type of cancer, as it accounts for 30% of cancer cases detected in women. Again, 15% of cancer deaths in women are related to breast cancer (Siegel *et al.*, 2020). Breast cancer incidence rates are disproportionately high in developing countries around the world: According to estimates, the number of newly diagnosed cases increases by 55%, and the mortality rate increases by 58% within 20 years (Villarreal-Garza, 2013). In a study conducted in Turkey, it was reported that in 2019, about 4300 women died from breast cancer (Bora Bashara *et al.*, 2021). Breast cancer, the incidence of which is gradually decreasing among women, occurs in every fourth woman diagnosed with cancer.

These statistics emphasize a significant reduction, early diagnosis and treatment of bile. Regular medical examination, mammography, self-examination of the mammary glands and education about the disease and reducing the risk of the disease can help in the detection of breast cancer at the stage of the disease, which improves the prognosis of the disease more effectively.

Breast cancer is the most common type of cancer in women worldwide and is a serious health problem. While early diagnosis increases the curability of breast cancer, treatment options may be limited, and the mortality rate increases in cases diagnosed at late stages. Therefore, the development of effective screening methods for the early diagnosis of breast cancer has great importance.

Цель: The purpose of this article is to study methods of screening and early diagnosis of breast cancer, as well as to evaluate the progress achieved in this area. The importance of breast cancer screening and early diagnosis will be emphasized, and the advantages and disadvantages of modern methods will be discussed. In addition, the potential of new technologies and approaches to the diagnosis of breast cancer will be discussed, and future areas of research and development in this area will be highlighted.

Method: This article is based on a literature review and review. Data obtained from reliable sources, such as scientific publications, academic sources and official reports of health care institutions, were studied. Methods of screening and early diagnosis of breast cancer are discussed in detail, how these methods work, in which population groups they are used and how effective they are.

Scope: The purpose of this article is to comprehensively enlighten the process of screening and early diagnosis of breast cancer. Methods used in breast cancer screening will be discussed in detail, especially imaging methods such as mammography, ultrasound, magnetic resonance imaging (MRI), and biomarkers such as recently developed molecular markers. Practical problems and limitations of using these methods will also be discussed.

Limitations: This article is based on information collected from available literature and sources. Therefore, the scope of the article and the topics it covers may be limited depending on current information and research in the literature. In addition, since developments in the field of screening and early diagnosis of breast cancer are developing at a rapid pace, they may not reflect the latest achievements at the time of writing. Considering these limitations, the article is designed to give a general idea of screening and early diagnosis of breast cancer.

2. Breast cancer risk factors

Approximately every eighth woman risks developing breast cancer during her lifetime, and many factors influence this process (Ministry of Health, 2021). During the study of the incidence of breast cancer in the eastern and western regions of Turkey, it was established that breast cancer is diagnosed twice as often in the west. It has been established that this may be due to differences in nutrition and lifestyle of women in both regions, variable period of lactation and use of hormone replacement therapy (Ozmen V., 2013). It was noted that the morbidity and mortality associated with breast cancer can be reduced in these women, especially by identifying women at risk of developing breast cancer and ensuring their regular participation in cancer screenings (Enjezab, 2016). Among the risk factors of breast cancer, age, reproductive history, gene mutation that increases the risk of breast cancer, dense structure of the breast, female sex and family history of breast cancer do not depend on the person (Haschemian *et al.*, 2016; Khushalani *et al.*, 2020). Nevertheless, it is possible to prevent the development of breast cancer or increase survival with the help of early diagnosis, supporting these people in adopting a healthy lifestyle and regular participation in cancer screening programs. A sedentary lifestyle, alcohol and cigarette consumption, postmenopausal obesity, consumption of exogenous hormones, such as oral contraceptives and hormone replacement therapy, as well as the lactation period are considered controllable risk factors (Drost *et al.*, 2018; Hansen, 2017).

Among the risk factors for the occurrence and development of breast cancer, some of the most important ones stand out.

- **Heredity:** If there are cases of breast cancer in the family history, the risk of developing breast cancer increases 2-3 times. Special attention should be paid to the analysis of BRCA1 and BRCA2 mutations, which can significantly increase the risk of developing breast and ovarian cancer. The detection of these mutations allows you to adjust the frequency of examinations for these types of cancer.
- **Reproductive factors:** Early onset of menstruation, late menopause and late birth of the first child are reproductive risk factors. This is due to the long-term effect of estrogens on the mammary gland. Long-term use of oral contraceptives and replacement hormone

therapy can also increase the risk. On the other hand, breastfeeding has a protective effect.

- **Other factors:** Excessive alcohol consumption, excess weight and obesity, as well as physical inactivity are other factors of the risk of developing breast cancer. These factors are the main ones in 21% of breast cancer deaths in the world. In high-income countries, the main factor is overweight and obesity, while in low- and middle-income countries, physical inactivity has a greater influence (10%).

Prevention and early detection of breast cancer:

- **Prevention:** The principles of healthy nutrition, increasing physical activity, combating alcohol consumption, overweight and obesity contribute to reducing the risk of developing breast cancer in the long term.
- **Self-examination of the mammary gland:** In 70% of cases, pathological changes in the mammary gland are detected by women themselves during self-examination. This method has low sensitivity, however, it is an important part of breast cancer prevention, since doubts that arise during self-examination are a reason to consult a doctor and conduct more detailed studies. Self-examination should be carried out according to a certain scheme and regularly on certain days of the cycle.
- **Mammography or ultrasound:** Mammography is an effective screening method for early detection of breast cancer. If mammography is impossible for certain reasons, ultrasound can be used. Over the past 50 years, mortality from breast cancer among women in countries where screening coverage exceeds 70% has decreased by 20-30%.
- **Diagnosis:** The final diagnosis of "breast cancer" can be made only after the histological examination of the biopsy of the tumor and nearby tissues of the breast. This diagnostic method is recognized as the "gold standard" in the diagnosis of oncological diseases.

In the development of breast cancer, the hereditary factor plays a role in approximately 5-10% of cases of the disease. The hereditary form of cancer is most often diagnosed in young women of reproductive age (Letyagin, 2004). Clinical observations show that the presence of relatives with breast cancer significantly increases the risk of developing the disease. In connection with this, a special form of pathology was identified - breast cancer, within which there may be various genetically determined variants. The authors do not exclude the possibility of the presence in the population of two forms of breast cancer - hereditary and sporadic.

Based on the study of individual genealogical lines, the following criteria were proposed for the detection of "hereditary" breast cancer:

- **Early age of onset of the disease:** People suffering from "hereditary" breast cancer usually develop it at a younger age than people without a family predisposition to this disease.
- **Bilateral lesion:** Unlike occasional cases of breast cancer, in which unilateral lesions are more common, people with "hereditary" breast cancer have a significantly increased risk of developing cancer in both breasts.

- **"Vertical" transmission of the disease:** With "hereditary" breast cancer, it is possible to observe the transmission of genetic changes from one generation to another. This means that people with a family predisposition to breast cancer have a higher risk of getting the disease if there have already been cases of breast cancer in their family.
- **The presence of specific tumor associations:** In people with "hereditary" breast cancer, there may be an association between breast cancer and other types of cancer, such as ovarian cancer or pancreatic cancer. This may indicate the presence of an inherited genetic mutation that predisposes to the development of various types of cancer.
- **Improved patient survival:** Research shows that people with "hereditary" breast cancer may have a better prognosis than cases of accidental breast cancer. This may be due to early detection and more active monitoring in people with a family predisposition to breast cancer.

It is important to note that these criteria are not unambiguous and defining for "hereditary" breast cancer. Diagnosis and determination of the risk of development of this type of cancer require a detailed medical examination and consultation with genetic specialists.

In 1993, Ya.V. Bohman conducted a study on a large clinical material to study the role of genetic predisposition in the development of cancer of different localization. It turned out that the risk of developing this disease in blood relatives of breast cancer patients was 3-5 times higher than in the female population as a whole. Family background research revealed a relationship between ovarian cancer, endometrial carcinoma, and breast cancer. It was also found that breast cancer, ovarian cancer and colon cancer often occur in relatives of patients with endometrial cancer. Currently, it is recognized that the earlier manifestation of cancer is the main symptom of all hereditary forms of neoplasia, including breast cancer. This is due to the mutation that occurs already in germ cells and additional somatic mutations are required for its manifestation. In the case of hereditary cancer, all tissues carry a "pathological" gene, so it is characterized by primary multiple lesions. Connections between breast cancer and cancer of the gastrointestinal tract, breast cancer and ovarian cancer, breast cancer and tumors of soft tissues, brain, tongue and larynx, as well as with adrenal cortex adenoma (SBLA syndrome) were revealed. Different relationships with tumors indicate the genetic heterogeneity of breast cancer. One of the important achievements in molecular genetic research of breast cancer was the discovery of BRCA1 and BRCA2 genes, the mutations of which are inherited and associated with the hereditary form of this tumor. Inherited mutations of these genes cause from 56% to 80% lifetime risk of developing breast cancer. (Nemtsova *et al.* 2003; Kharchenko *et al.* 2006). The spectrum of BRCA1 gene mutations includes a wide range: 71% of mutations are associated with a change in the reading frame caused by micro- and mini-deletions. The BRCA1 gene is located at site 17q21.1-21.2. Loss of BRCA1 expression is associated with increased proliferation and increase in the size of the tumor node.

The second genome-suppressor, which has greater specificity for breast cancer, is the BRCA2 gene. The mutation of this gene plays an important role in the

development of hereditary cases of breast cancer in both men and women (Letyagin, 2004). In addition to the hereditary factor, the hyperproduction of estrogens, the formation of their reactive metabolites, and changes in the reception of these hormones by target cells also play an important role in the development of breast cancer. It is believed that under the influence of estrogens, the expression of some proto-oncogenes in target cells, including the c-fos, c-myc, c-jun genes, and the formation of cyclins, cyclin-dependent kinases, autocrine and paracrine growth factors and their receptors are stimulated (Garin, 2005; Nasedkina, 2006; Stewart *et al.* 1992^[6]). Studies show that the promotion process in breast cancer, as well as other tumors, is associated with the activation of the estrogen receptor system. Estrogen-induced growth factors can have autocrine or paracrine effects. Receptors of polypeptide growth factors belonging to the ERBB family are expressed on cell membranes, and ERBB2 or HER2/neu are particularly important. As a result of intensive hormonal stimulation of estrogen receptors in the mammary gland, there is an increase in the formation of transforming growth factor alpha (TGF- α), which belongs to the family of growth factors EGF (epidermal growth factor). TGF- α stimulates mitotic activity and growth of tumor and normal cells of epithelial origin, and also has angiogenic properties (Garin, 2005; Bacon, 1998^[7]; Lippman *et al.* 1988^[8]; Schreiber, 1986^[9]). At the same time, the formation of the estrogen-receptor complex induces the synthesis of insulin-like growth factor and inhibits the formation of transforming growth factor beta (TGF- β). TGF- β belongs to the EGF family, and it slows down the division of tumor and normal cells, and also promotes their differentiation (Letyagin, 2004; Moses, 1990^[10]; Roberts and Spon, 1993^[11]; Zugmaier and Lippman, 1990^[12]).

Breast stroma cells, due to the release of fibroblastic growth factor, stimulate their own proliferation and growth of paracrine-epithelial tumor cells. The platelet-derived growth factor also contributes to the proliferation of the mesenchymal stroma of tumors (Garin, 2005; Gershtein and Kushlinsky, 1998; Dickson and Lippman, 1995^[14]). It is important to note that a significant part of cells that have undergone oncogenic transformation die in the early stages of promotion as a result of apoptosis. One of the characteristic features of the effect of estrogens on target cells is that they suppress apoptosis with the participation of the oncogene BCL-2 (Kovalenko *et al.* 1997). According to some studies, estrogens contribute to the accumulation of microsatellite DNA structures in target cells, which can be considered as a manifestation of defective DNA damage repair. It was also shown that not only sex hormones have oncogenic activity, but also the products of their transformations, including products of 2-hydroxylation, 16-alpha-hydroxylation and 4-hydroxylation, known as catecholestrogens. In the mechanisms of oncogenic transformation of the epithelium of mammary glands, the strengthening of the process of 16-alpha-hydroxylation of estrone is of special importance (Kovalenko *et al.* 1997; Bohman *et al.* 1997).

Some studies show that the activity of enzymes responsible for the metabolism of estrogens - catechol-O-methyltransferase and glutathione-S-transferase, significantly decreases in metastases of hormone-dependent tumors of the breast. This leads to the accumulation of highly active estrogen derivatives, which have a mutagenic

effect and contribute to the development of a more aggressive phenotype of tumor cells (Kondakova *et al.* 2005). The role of increased content of free estradiol in the blood, especially noticeable in women during menopause, in the mechanisms of breast cancer is increasing. Potentially carcinogenic promoters of breast cancer can be oral contraceptives and hormonal preparations used in replacement therapy during menopause.

Studies show that after the menopause, there is a decrease in the level of estrogen in the blood, and then a slow increase due to the intracellular conversion of androstenedione into estrone with the help of the aromatase enzyme. This process of transformation of adrenal androgens occurs in adipose tissue, liver, muscles and mammary gland tissue (Podubnaya, 2006). As a result, the ratio of separate fractions of estrogens changes, where estrone prevails over estradiol. This knowledge led to the idea that one of the effective methods of treating breast cancer in the postmenopausal period is the use of aromatase inhibitors (Letyagin, 2004; Ognerubov *et al.* 1998; Podubnaya, 2006).

One of the leading risk factors for the development of breast cancer is hypothyroidism, which can be both hereditary and acquired. The level of thyroid hormones affects the conversion of estradiol fractions of estrogens into estrone. In conditions of hypothyroidism, there is an increased conversion of estradiol fractions (Bershtein, 2000; Garin, 2005). It is also proven that a decrease in the optimal level of thyroid hormones leads to the stimulation of the growth of epithelial cells of the mammary glands, the development of dysplasia and neoplasia.

Some researchers express the opinion that increased production of insulin-like growth factor I (IGF) is one of the key factors in the risk of developing breast cancer. Receptor IPFR plays an important role in cell division, and its increased expression leads to neoplastic transformation of cells (Garin, 2005). It is assumed that insulin also plays an important role in the regulation of mitogenic activity of cells and promotes the development of the promotional stage of tumor growth. Therefore, hyperinsulinemia is considered as a risk factor for the development of a number of tumors.

One of the main mechanisms of protection against tumor cells is the activation of cellular immunity with the help of CD8-T-lymphocyte-killers and lymphokine producers. The risk of developing neoplasia, including breast cancer, increases significantly with T-dependent immunodeficiency. Insufficiency of specific mechanisms of anti-tumor immunity can be connected not only with previous pathology of infectious and non-infectious nature, stress factors, but also with biological features of the tumor. The latter may be associated with the variability of tumor cells during tumor progression, including a decrease in the expression of class I histocompatibility antigens. Transformed cells are able to avoid the cytotoxic effect of CD8-T-lymphocytes, which are able to recognize only oncogenic antigens in connection with MHC class I proteins. The importance of B-dependent immunodeficiency in the induction and promotion of neoplasia is ambiguous due to the heterogeneity and reactogenicity of the cellular composition of the immune system, which is constantly exposed to various external and internal stimuli. It is known that the amount of immunoglobulins in tumor tissue can exceed the level in normal tissue, while the content of immunoglobulins in the blood of cancer patients is greatly

reduced.

In addition to the above-mentioned risk factors for the development of breast cancer, such as genetic predisposition, age, hormonal and immune status disorders, previous oncological diseases, there are other diseases of the breast that refer to precancerous conditions. These conditions include fibroadenoma, mammary gland cyst, intraductal papilloma, diffuse form of fibrocystic mastopathy and other forms of pathology. It should be noted that the activation of lipoperoxidation processes, free radical disorganization of cells of various organs and tissues plays an important role in the mechanisms of oncogenic transformation of cells, disruption of intercellular interaction and metastasis of malignant cells in various forms of precancerous conditions, including breast diseases.

3. Breast cancer screening

Breast cancer is an important public health problem and is included in the cancer screening program because it can be diagnosed at an early stage. In this context, as stated by the World Health Organization (WHO), the type of cancer must have certain characteristics so that it can be screened.

These particularities;

- To be a common disease in society
- High selectivity of screening tests for this disease
- Acceptable and simple application of screening tests for people
- Availability of adequate extended methods of examination and treatment of pathologies revealed by the results of scanning.
- There should be recommendations and medical data about the clinical course of the disease.
- Periodic scans must be repeated (WHO, 2018).

Cancer of the breast gland is a progressive disease, and the expected life expectancy is higher, because with early diagnosis, the probability of its cure is higher. It is extremely important to diagnose the tumor before it becomes palpable (Smith *et al.*, 2010). In developed countries, the 5-year survival rate of patients diagnosed with breast cancer with early diagnosis and treatment methods is approximately 90-95% (Fahad, 2019). In breast cancer, the stage at the time of diagnosis is important for the patient's survival. In the conducted studies, it was established that the survival rate is significantly higher in women whose breast cancer was diagnosed as part of the screening program, and this is where the value of early diagnosis is shown (Evans *et al.*, 2021). Risk factors such as age, family history of breast cancer, genetic and environmental factors, obesity, alcohol consumption, radiation exposure, breastfeeding status and menopause, fertility status, history of breast cancer, and benign breast disease should be considered. как междисциплинарный, и патияны будуны программы. with breast cancer, it is necessary to be guided (Coughlin, 2019).

With the help of breast cancer screening methods, 63.7% of breast cancer can be diagnosed in the early localized period. Thus, breast cancer is the type of cancer with the best prognosis and the longest life expectancy among the most common types of lung, colon and stomach cancer in the world (American Cancer Society, 2022). However, in this situation, another problem arises, for example, the high life expectancy of cancer patients. At the moment, screening programs are the basic element of early diagnosis, and when

conducting oncological screening of patients at certain intervals in accordance with the standards, the disease will be detected and brought under control at its localization, and the quality of life of the sick person will be high (World Health Organization, 2021.).

4. Conclusions and suggestions

Today, the survival of patients with breast cancer has increased thanks to the development of pharmacological treatment methods, increased clinical experience in the field of breast cancer, and advanced imaging systems. In addition, our goal should be that a person can recover from this disease with the least psychological, physical, social and financial losses through early diagnosis and treatment without the need for long-term treatment protocols. In this context, doctors working in primary health care institutions must inform and guide their patients registered in their departments about the appropriate screening methods. Again, in primary health care, nurses and midwives must motivate patients to self-examine their mammary glands. Public medical centers must organize trainings for various sections of society to raise awareness of breast cancer. Medical workers working in the field of secondary and tertiary medical care must encourage patients from the risk group to go to the appropriate departments for breast cancer screening.

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