

**THE QUESTION OF MALE BREAST CANCER**

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**ABSTRACT**

Male breast cancer (BC) is a rare disease, accounting for approximately 1% of all breast cancer cases diagnosed worldwide. Studies of breast cancer in men are significantly inferior in scale to the corresponding studies in women. This article presents a review of the literature in terms of understanding the prevalence, risk factors, etiology, diagnosis, treatment, and genetic predisposition of breast cancer in men.

**KEYWORDS:** Breast cancer, Men, BRCA1 and BRCA2 genes.

**INTRODUCTION**

Breast cancer (BC) in men is a rare disease. Male breast cancer accounts for approximately 1% of all diagnosed breast cancer cases worldwide. According to the Robert Koch University of Berlin, 400 cases of male breast cancer are diagnosed every year in Germany. In 2008, about 500 diseases were detected in men in Russia for 52,469 new cases of breast cancer.<sup>[2]</sup> According to the Surveillance, Epidemiology and End Results (SEER) registry, from 1973 to 2005, 5494 cases of breast cancer were registered in men and 835000 in women.<sup>[24,25]</sup> Men get sick, on average, ten years later than women, most often in the 6th-7th decades of life, although this pathology occurs at the age of 9 to 90 years or more. In the United States, in recent years, the incidence of breast cancer in men has increased in proportion to the increase in the age of the patient. The peak incidence in men is approximately 75 years old, while in women, the age indicator has 2 peaks of manifestation: early and late. In representatives of the Negroid race, the incidence is slightly higher than among white men, regardless of age: the prevalence of the disease among white men is 1.1 cases per 100 thousand of the population, while among the Negroid race it is 1.8 cases per 100 thousand.<sup>[6]</sup> If we compare this indicator in women, then in black women the incidence is lower than among white women, the only exception is the age category under 40 years old. Information from the database of the Association of Nordic Cancer Registries (NORDCAN) indicates a downward trend in age-standardized mortality from breast cancer in both men and women.<sup>[19]</sup>

Compared with women, breast cancer in men more often has clinical signs characteristic of the later stages of the disease. In approximately 20% of cases, the diagnosis of breast cancer in men is not established during the initial visit. Also noteworthy is the fact that 46.8% of patients

have a significant local spread of the process during the initial treatment.<sup>[1,4]</sup> As a rule, this is a primary tumor larger than 2 cm, possibly with ulceration, and the presence of metastases in the axillary lymph nodes. Most often, the tumor is localized in the central parts of the gland, so about half of the patients at the time of treatment have a symptom of "nipple retraction". Tumor fixation to the pectoralis major muscle is rare.<sup>[3]</sup>

Risk factors for breast cancer in men are: race, age, genetic predisposition to this disease. Among studies conducted in the United States, higher incidence and mortality from breast cancer in men living in northern latitudes than those living in southern and southwestern regions. There are reports of the appearance of breast cancer in men 20-25 years after exposure to intense ionizing radiation, as well as in patients who received radiation therapy for Hodgkin's lymphomas or other diseases of the chest and mediastinum. Such potential risk factors as hormonal, comorbidities (cardiovascular disease, liver disease, diabetes mellitus), environmental factors are less reliable, since they were identified mainly in case-control studies. Some studies indicate a relationship between breast cancer in men and elevated levels of estradiol. Thus, cirrhosis of the liver, obesity, as well as the intake of estrogens from outside, which increase the level of circulating estrogens, may be associated risk factors for this disease.<sup>[23,30]</sup> There may be a relationship between the risk of developing breast cancer and testicular dysfunction, which can lead to an imbalance between androgens and estrogens.

In about 30-70% of cases, breast cancer in men develops against the background of gynecomastia, in particular its nodular form. Gynecomastia i.e. increased development and growth of the mammary glands in men is a common disease among adolescents and, in terms of its clinical

and morphological features, occupies an intermediate position between the physiological state and proliferative processes. The incidence of cancer against the background of proliferative forms of gynecomastia depends on the duration of the disease and the period of observation of the patient. The risk of transition of the nodular form to cancer ranges from 9.3 to 12.2%.<sup>[4]</sup>

About 15-30% of men have a positive family history of breast or ovarian cancer. Male carriers of a mutation in the BRCA2 gene have a lifetime risk of developing breast cancer of 6%, which is 150-200 times higher than in the general population, while female carriers of a mutation in the BRCA2 gene have a lifetime risk of developing breast cancer. 50-85%, ovarian cancer - 10-20%.<sup>[14,22,32,34]</sup> Mutations in the BRCA1 gene are less closely associated with breast cancer in men.<sup>[10,13,31]</sup> The risk of mutations in this gene in males is 1-5%.<sup>[11]</sup> In studies conducted in families with familial breast cancer, structural rearrangements in the BRCA2 gene were found in men in 76% of cases, mutations in the BRCA1 gene in these families were found in 16% of cases.<sup>[5]</sup>

The diagnostic algorithm for breast cancer in men includes a primary examination of the gland and regional zones, mammography and ultrasound, tumor biopsy for the purpose of cytological and histological examination of the material, as well as determining the level of steroid hormone receptors, the degree of proliferative activity of the tumor and the presence of Her2 / neu receptors. In men suffering from breast cancer, such a histological type as invasive ductal cancer mainly prevails (85-95%),<sup>[25]</sup> however, there are cases of invasive lobular cancer and ductal cancer in situ. Data on molecular subtypes of breast cancer in men are practically absent today, since the only source of information is several single-center studies, the results of which should be considered as preliminary, due to the small number of cases.

In all cases of breast cancer in men, it is necessary to examine the content of estrogen and progesterone receptors in the tumor. Almost all studies indicate the presence of higher levels of estrogen receptors in men than in women. Clinically significant levels of estrogen receptors in the tumor are present in approximately 75% of patients, and progesterone receptors are present in 43% of patients.<sup>[4]</sup> The presence of receptor-positive tumors in men does not increase with age, as it does in women.

Currently, there is an active search for factors that would predict the course of breast cancer in men. One of the most important prognostic factors in male breast cancer is the presence of c-erbB-2 (Her2/neu) oncoprotein expression and Ki-67 proliferative activity index. Information on the expression of Her2/neu by breast cancer cells in men is very contradictory. Bloom et al. reported that, according to immunohistochemical analysis, overexpression of the Her2/neu gene was

detected in 1 (1.7%) of 58 cases, and amplification of the Her2/neu gene according to the data of fluorescence in situ hybridization was absent in all cases.<sup>[9]</sup> According to the European Institute of Oncology (IEO), the Her2/neu gene expression frequency is 15%.<sup>[16]</sup> The Ki-67 criterion has already found its application in breast cancer in women, but its role in the prognosis of cancer in men has not been fully elucidated and requires further study.

The main in the treatment of breast cancer in men is surgical treatment in the amount of radical mastectomy with preservation of the pectoral muscles. However, it should be noted that at the neoadjuvant stage, radiation therapy and chemotherapeutic treatment are possible. Anthracycline-containing drug regimens are mainly used in combination with hormone therapy (for a receptor-positive tumor) or with radiation therapy using coarse fractionation methods. The most significant risk factor for both local recurrence and distant metastases is axillary lymph node involvement, which occurs in almost 50% of men with breast cancer. In 40% of cases, the number of affected lymph nodes exceeds 3.<sup>[1,15,17,21,25,27,29]</sup>

Only a few studies have been devoted to studying the effectiveness of radiation therapy after mastectomy.<sup>[12,17]</sup> and according to their results, when evaluating the indications for radiotherapy, it is necessary to follow the recommendations for the treatment of this disease in women. Additional indications for locoregional radiotherapy should be the location of the tumor in the central region and its spread to the underlying muscles.

Adjuvant polychemotherapy in men with breast cancer is associated with risk factors such as young age, a high degree of malignancy, and the presence of axillary lymph node metastases. In most cases, combinations of regimens with the inclusion of anthracyclines are used, but taxanes can also be used.<sup>[18,33]</sup> The main direction of systemic treatment of breast cancer in men with positive levels of hormone receptors is endocrine therapy. To date, Tamoxifen is the main drug used for breast cancer in men.<sup>[25]</sup> Aromatase inhibitors should be considered second-line hormonal therapy.<sup>[1,4]</sup>

It is worth highlighting the particular complexity of the treatment of disseminated forms of breast cancer in men. The main therapeutic measures in such cases remain chemo-endocrine therapy and radiation therapy to the lesions. Trastuzumab therapy should be considered in addition to hormone therapy or chemotherapy in patients with high expression or amplification of the Her2/neu gene. Preparations of the bisphosphonate group reduce the risk of pathological fractures due to bone metastases and are most effective in the event of hypocalcemia.

Survival studies for breast cancer in men are significantly inferior in scale to the corresponding population-based studies involving women. In most cases, only the overall survival of men with this

pathology was assessed. According to the literature of recent decades, the 5-year survival rate of men with breast cancer ranges from 36 to 66%.<sup>[25]</sup> the 10-year survival rates for stage I–IIa of the disease are 91.5%, for stage IIb - 72.5%, for stage III - 44.2%, at stage IV they do not exceed 3.2%.<sup>[4]</sup>

Despite the similarities with breast cancer in women, there are still many open questions in the study of this disease in men. There appear to be racial and ethnic differences in disease prevalence and survival, but these observations require further confirmation. Risk factors for breast cancer in men can be clarified in further larger studies on the prognostic significance of various biological markers. It is difficult to come to a conclusion regarding the influence of the c-erbB-2 (Her2/neu) proto-oncogene expression factors and the Ki-67 proliferative activity indicator due to their insufficient knowledge regarding breast cancer in men. The question of the prevalence of molecular biological subtypes of this pathology also remains open. The most interesting is the presence of a genetic component of the disease in men. In the domestic literature, this issue is not covered in sufficient detail, and there have been practically no studies on genetic predisposition. Works related to clinical and genotypic correlations of BRCA-associated breast cancer in men are rare. In foreign literature, data on genetic predisposition vary significantly. Thus, it can be concluded that the problem of breast cancer in men remains very relevant for study both from a clinical and genetic point of view.

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