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Relevant Concepts of the Development Mechanisms, Systematization, and Therapeutic-Associated Risk Factors of Momentary Cancer (Literature Review)

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Abstract: Breast cancer is one of the most pressing problems in modern oncology, occupying a leading position in the structure of oncological morbidity among women worldwide and accounting for approximately 30% of all malignant neoplasms in women. According to the World Health Organization, more than 2.3 million new cases of breast cancer are registered annually worldwide, making this disease a global public health problem requiring a comprehensive interdisciplinary approach to its study, diagnosis, and treatment.

Keywords: lymphedema, breast cancer, axillary lymph node dissection, radiotherapy, risk factors, quality of life

Introduction Breast cancer is one of the most pressing problems in modern oncology, occupying a leading position in the structure of oncological morbidity among women worldwide and accounting for about 30% of all malignant neoplasms in women. According to the World Health Organization, more than 2.3 million new cases of breast cancer are registered annually worldwide, making this disease a global public health problem requiring a comprehensive interdisciplinary approach to its study, diagnosis, and treatment [1]. In recent decades, fundamental changes have occurred in understanding the molecular-biological basis of breast carcinoma development. Modern studies show that this disease is not a single nosological form, but a heterogeneous group of tumors with different molecular characteristics, biological behavior, prognostic factors, and sensitivity to various types of therapy. Revolutionary discoveries in the field of molecular oncology, including the identification of the BRCA1/BRCA2 genes, the study of the role of estrogen, progesterone, and HER2/neu receptors, as well as the development of the concept of molecular subtypes of breast cancer, have fundamentally changed approaches to the diagnosis, prognosis, and treatment of this disease[2].

The pathogenesis of breast carcinoma is a multifactorial process, including the complex interaction of genetic, epigenetic, hormonal, environmental, and lifestyle factors. The modern concept of carcinogenesis considers the development of breast cancer as a multi-stage process, including the initiation, promoting, and progression of the tumor, in which normal breast epithelial cells sequentially acquire malignant properties through the accumulation of genetic and epigenetic changes. The disruption of tumor suppressor genes, oncogenes, and DNA repair genes, as well as the disregulation of signaling pathways that control cell proliferation, apoptosis, and DNA repair, plays a key role in this process[3].

The modern classification of breast carcinoma is based on the integration of the tumor's morphological, immunohistochemical, and molecular genetic characteristics. Histological classification distinguishes various morphological variants, including invasive carcinoma of the non-specific type, invasive lobular carcinoma, mucinous, medullary, tubular, and other specific types.

Molecular classification based on the expression of estrogen (ER) receptors, progesterone (PR), HER2 protein, and Ki-67 proliferation index identifies the main molecular subtypes: luminal A, luminal B, HER2-positive, and triple negative, each characterized by specific biological features and requiring individualized therapeutic approach[4].

Risk factors for breast cancer development are traditionally divided into non-modifiable (age, gender, genetic predisposition, family history) and modifiable (reproductive factors, hormonal influences, lifestyle, nutrition, physical activity). In recent years, special attention has been paid to studying therapeutically associated risk factors that may arise as a result of ongoing treatment of the underlying disease or comorbidities. This category includes ionizing radiation during radiation therapy for other malignant neoplasms, prolonged use of hormone replacement therapy, some chemotherapeutic drugs, and immunosuppressive therapy[5].

The development of personalized medicine has led to fundamental changes in approaches to treating breast carcinoma. Modern therapy is based on the molecular characteristics of the tumor and includes surgical treatment, chemotherapy, hormone therapy, targeted therapy, and radiation therapy. The introduction of targeted drugs, including trastuzumab, pertuzumab, T-DM1, CDK4/6 inhibitors, mTOR and PARP inhibitors, significantly improved the prognosis for patients with various molecular subtypes of the disease. However, along with achievements in the treatment of breast carcinoma, new problems arise related to the long-term consequences of therapy and the development of secondary malignant neoplasms. The study of therapeutically associated risk factors is particularly relevant in the context of increasing patient life expectancy and the need to assess the benefit/risk ratio of various therapeutic approaches[6].

Genetic testing and counseling have become an integral part of managing patients with breast cancer, especially if there is a family history of the disease or at an early age of manifestation. Detection of mutations in BRCA1, BRCA2, TP53, PALB2, ATM genes and other predisposition genes allows not only to assess the individual risk of disease development but also to choose the optimal therapeutic strategy, including the use of PARP inhibitors and preventive surgical interventions.

Epidemiological studies of recent years have shown changes in the structure of breast carcinoma morbidity, including an increase in the incidence of the disease in young people, an increase in morbidity in developing countries, and changes in the distribution of molecular subtypes. These trends require a review of existing approaches to disease prevention, screening, and treatment[7].

This review is aimed at systematizing modern knowledge about the pathogenetic mechanisms of breast carcinoma development, current classification approaches, and therapeutically associated risk factors, which is necessary for optimizing diagnostic and therapeutic strategies in clinical practice.The lymphatic system plays a crucial role in fluid homeostasis, immune surveillance, and lipid transport. However, current understanding of lymphatic physiology remains incomplete, limiting effective prevention and treatment of lymphatic disorders. Lymphedema is a chronic disease characterized by impaired lymphatic drainage and progressive accumulation of protein-rich interstitial fluid, most commonly affecting the extremities[8].

Lymphedema is associated with significant physical disability, recurrent infections, skin changes, chronic pain, and psychological distress. In advanced stages, long-standing lymphedema may lead to lymphangiosarcoma (Stewart–Treves syndrome), emphasizing the seriousness of this condition. With increasing survival rates in breast cancer patients, post-treatment complications such as lymphedema have gained growing clinical importance.Lymphedema is defined as a chronic progressive condition resulting from structural or functional impairment of the lymphatic system, leading to inadequate lymph transport and interstitial fluid accumulation. The hallmark clinical manifestation is persistent edema caused by lymphatic system damage. Beyond fluid retention, lymphedema induces inflammatory responses, adipose tissue deposition, fibrosis, and immune dysfunction. Because the lymphatic system is integral to immune defense, affected tissues are particularly prone to recurrent infections such as cellulitis and lymphangitis[9].

Primary lymphedema is a rare hereditary condition associated with congenital abnormalities of lymphatic vessels or lymph nodes. Its incidence ranges from 1–3 per 10,000 births, with a female predominance. Genetic mutations affecting lymphangiogenesis—such as VEGFR-3, FOXC2, GATA2, and others—have been identified in 25–30% of cases. Breast cancer treatment frequently involves axillary lymph node dissection (ALND) and regional radiotherapy, both of which disrupt lymphatic drainage of the upper extremity. Postmastectomy lymphedema significantly reduces upper limb function and negatively affects psychosocial well-being. Reported prevalence of BCRL varies widely, from 5% to nearly 50%, depending on diagnostic criteria and follow-up duration. Meta-analyses suggest an average incidence of approximately 21–30% after radical breast cancer treatment[10].

Breast cancer is one of the most pressing problems in modern oncology, occupying a leading position in the structure of oncological morbidity among women worldwide and accounting for about 30% of all malignant neoplasms in women. According to the World Health Organization, more than 2.3 million new cases of breast cancer are registered annually worldwide, making this disease a global public health problem requiring a comprehensive interdisciplinary approach to its study, diagnosis, and treatment. In recent decades, fundamental changes have occurred in understanding the molecular-biological basis of breast carcinoma development. Modern studies show that this disease is not a single nosological form, but a heterogeneous group of tumors with different molecular characteristics, biological behavior, prognostic factors, and sensitivity to various types of therapy. Revolutionary discoveries in the field of molecular oncology, including the identification of the BRCA1/BRCA2 genes, the study of the role of estrogen, progesterone, and HER2/neu receptors, as well as the development of the concept of molecular subtypes of breast cancer, have fundamentally changed approaches to the diagnosis, prognosis, and treatment of this disease [11].

The pathogenesis of breast carcinoma is a multifactorial process, including the complex interaction of genetic, epigenetic, hormonal, environmental, and lifestyle factors. The modern concept of carcinogenesis considers the development of breast cancer as a multi-stage process, including the initiation, promoting, and progression of the tumor, in which normal breast epithelial cells sequentially acquire malignant properties through the accumulation of genetic and epigenetic changes. The disruption of tumor suppressor genes, oncogenes, and DNA repair genes, as well as the disregulation of signaling pathways that control cell proliferation, apoptosis, and DNA repair, plays a key role in this process [12].

The modern classification of breast carcinoma is based on the integration of the tumor's morphological, immunohistochemical, and molecular genetic characteristics. Histological classification distinguishes various morphological variants, including invasive carcinoma of the non-specific type, invasive lobular carcinoma, mucinous, medullary, tubular, and other specific types. Molecular classification based on the expression of estrogen (ER) receptors, progesterone (PR), HER2 protein, and Ki-67 proliferation index identifies the main molecular subtypes: luminal A, luminal B, HER2-positive, and triple negative, each characterized by specific biological features and requiring individualized therapeutic approach [13].

Risk factors for breast carcinoma development are traditionally divided into unmodifiable (age, gender, genetic predisposition, family history) and modifiable (reproductive factors, hormonal influences, lifestyle, diet, physical activity). In recent years, special attention has been paid to studying therapeutically associated risk factors that may arise as a result of ongoing treatment of the underlying disease or comorbidities. This category includes ionizing radiation during radiation therapy for other malignant neoplasms, prolonged use of hormone replacement therapy, some chemotherapeutic drugs, and immunosuppressive therapy. The development of personalized medicine has led to fundamental changes in approaches to treating breast carcinoma. Modern therapy is based on the molecular characteristics of the tumor and includes surgical treatment, chemotherapy, hormone therapy, targeted therapy, and radiation therapy. The introduction of targeted drugs, including trastuzumab, pertuzumab, T-DM1, CDK4/6 inhibitors, mTOR and PARP inhibitors, significantly improved the prognosis for patients with various molecular subtypes of the disease.

However, along with achievements in the treatment of breast carcinoma, new problems arise related to the long-term consequences of therapy and the development of secondary malignant neoplasms. The study of therapeutically associated risk factors is particularly relevant in the context of increasing patient life expectancy and the need to assess the benefit/risk ratio of various therapeutic approaches.Genetic testing and counseling have become an integral part of managing patients with breast cancer, especially if there is a family history of the disease or at an early age of manifestation. Detection of mutations in BRCA1, BRCA2, TP53, PALB2, ATM genes and other predisposition genes allows not only to assess the individual risk of disease development but also to choose the optimal therapeutic strategy, including the use of PARP inhibitors and preventive surgical interventions. Breast cancer-related lymphedema is a common, multifactorial, and often underestimated complication of cancer therapy. Surgical extent, radiation therapy, obesity, and postoperative complications are key determinants of risk. A comprehensive understanding of lymphatic pathophysiology and treatment-related factors is essential for prevention, early diagnosis, and effective management.

Conclusions: Thus, epidemiological studies of recent years demonstrate changes in the structure of breast carcinoma morbidity, including an increase in the incidence of the disease in young people, an increase in morbidity in developing countries, and changes in the distribution of molecular subtypes. These trends require a review of existing approaches to disease prevention, screening, and treatment. This review is aimed at systematizing modern knowledge about the pathogenetic mechanisms of breast carcinoma development, current classification approaches, and therapeutically associated risk factors, which is necessary for optimizing diagnostic and therapeutic strategies in clinical practice.

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