EMJ MS
EUROPEAN MULTIDISCIPLINARY JOURNAL OF MODERN SCIENCE
ISSN 2750-6274 https://emjms.academicjournal.io Volume: 14 | Jan-2023

Subtypes of Breast Cancer

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Annotation: Subtypes breast cancer, and also feature of a metastazirovaniye and illness recurrence are presented to survival of patients in article, and, as a result, at different subtypes. Features of diagnostics of the remote metastasises depending on a subtype breast cancer are considered. At division into subtypes breast cancer different approaches to treatment of so heterogeneous disease are necessary.

Keywords: breast cancer, subtypes breast cancer, feature of diagnostics and treatment.

Breast cancer (BC) ranks 1st among oncological diseases in women, and is also the 2nd cause of death after cardiovascular pathology. In the structure of oncological incidence of the female population in Russia, breast cancer occupies the first place, which amounted to 20.1% in 2010 [1]. The incidence of breast cancer is steadily growing every year by 1–2%, more than 1 million new cases are registered annually in the world, by 2020 the number of cases of breast cancer will be 2 million new cases.

The surgical method, both in an independent version and in combination with radiation therapy, chemo hormonal therapy, targeted therapy, is the basis of breast cancer treatment. For the diagnosis of breast cancer, new technologies are used to detect the disease at an early stage (digital mammography, magnetic resonance imaging of the mammary glands (BC) with contrast, elastography). It should be noted that in Russia over the past 10 years, the proportion of stages I-II of breast cancer has increased by 10% [2].

Even with the current level of knowledge, there are often cases when it is difficult to answer numerous questions: is it necessary to carry out adjuvant (neoadjuvant) therapy? If yes, which one and for how long?

The reason for such complex issues is the heterogeneity of breast cancer. This fact has been known for a very long time, but only recently the molecular basis of this heterogeneity has become clear. In fact, with one localization of the process in the breast, there are several diseases that differ in the causes of malignant growth, genetic disorders, clinical course, and different prognosis of the disease [3].

The end of the 20th century, marked by the determination of the genetic heterogeneity of breast cancer originating from different morphological clones of the tumor, made it possible to make the necessary adjustments to such an important prognostic criterion as the histological type. The importance of breast epithelial stem cells as an important target, subjected to local and systemic effects from the very early stages of oncogenesis, has become obvious. The dynamism inherent in the breast during pregnancy, lactation and involution is believed to have its source in 3 cell lines formed on the basis of stem cells: 1) myoepithelial or basal (outer) cells of the ducts and alveoli; 2) cells of the luminal (inner) lining of the ducts; 3) alveolar cells that synthesize milk proteins. Stem cells are capable of self-renewal and, under the influence of hormones and stromal epithelial interactions, can actively proliferate, differentiate during pregnancy and especially during lactation (which explains the

protective/antitumor role of feeding) and, conversely, undergo apoptosis during breast involution.

It turned out that some of the tumors originate from the luminal epithelium surrounding the ductal-lobular unit, and some from the basal epithelium, located outward from the luminal one. Moreover, in subsequent studies, the relationship between the origin of the tumor and clinical and prognostic characteristics, and most importantly, with a possible response to ongoing drug therapy, was established. Ultimately, these factors were the real basis for revising the existing classification of breast cancer, taking into account molecular and histological features.

Recognition of the role of stem cells as a material substrate of mammary carcinogenesis (including all hormone-dependent variants) was superimposed on at least 2 scientific achievements. One of them boiled down to an indication that breast cancer in carriers of BRCA1 mutations is often not only estrogen receptor-negative, but also predominantly (although this is sometimes disputed) originates from basal-type stem cells, which may also be related to the predisposition in this case to progenotoxic variant of hormonal carcinogenesis.

Another achievement is based on the involvement in the analysis of the so-called genetic "portraiting" (or profiling) of the tissue of mammary carcinomas. At the same time, using microarray analysis of complementary DNA in the tumor material, the expression of several thousand biologically significant genes was evaluated, the processing of which led to the isolation of several of the most typical and differing variants. These subtypes are luminal A, luminal B, triple negative (TN)/basal-like, HER2, and 5th "unclassified".

In fact, the classification itself is built on the basis of such characteristics as the progenitor cell (luminal or basal epithelium); the presence or absence of steroid receptors and HER2 receptors (ErbB-2) in the tumor, a receptor tyrosine kinase that is part of the epidermal growth factor family; proliferative potential; the presence or absence of cytokeratin 5/6, characteristic of myoepithelial (basal) cells. Such a division into types, not yet reaching the level of a standard procedure in medical practice, is reflected in the characteristics of the course of the disease. So, for example, according to the information provided, the luminal subtype A is characterized by the best prognosis, the highest survival of patients and a fairly low rate of recurrence of the disease, and vice versa, TN.

Breast cancer is characterized by high malignancy, an aggressive course of the disease and an unsatisfactory response to standard therapy. The luminal subtype B is closer in this respect to the luminal subtype A, and the subtype with overexpression of HER2 is closer to TH. Breast cancer is manifested by pronounced heterogeneity, which may be due to the presence or absence of steroid hormone receptors in the tumor, primarily estrogen and progesterone. As expected, one of the leading factors among these factors was the age of patients with a border, often passing at the turn of the end of the reproductive period and the onset of menopause. According to the materials provided by the Danish Breast Cancer Cooperative Group, the incidence of ER+PR+ neoplasms (about 63% of all observations) steadily increased with age, demonstrating a transient decrease only in the range of 43−47 years. The frequency of the opposite, receptor-negative, variant of tumors (ER-PR-), averaging 17.6%, increased up to 50 years, after which it remained unchanged. The proportion of the ER+PR– subtype (average 13.9%) increased quite rapidly immediately upon the onset of menopause, after which this increase slowed down. On the contrary, the incidence of rarely detected ER–PR+ tumors (5.6%) increased only up to the age of 43–45 years and then decreased [4].

A number of other works of this kind were considered by W. Anderson et al. (2006) not so much as a reflection of bimodality in the age-dependent distribution of breast cancer frequency, but as a confirmation of the long-held point of view that there are 2 main forms of

the disease: pre- and postmenopausal, which differ primarily in their estrogen dependence. As additional evidence, the authors relied on data on the distribution of individual morphological variants of breast neoplasms by age group, showing that intraductal, tubular and lobular carcinomas are characterized in this respect by two apexes, medullary ones often occur at an average age of about 40 years, and papillary and mucinous - at 65-70 years old. Comparing these observations with data on the detection of steroid hormone receptors in the same tumors, W. Anderson et al. (2006) found some agreement with their expectations, except for medullary carcinoma. However, extrapolating their results to the classification of breast cancer subtypes mentioned above, they concluded that the combined group of luminal neoplasms (luminal A and B) is characterized for Caucasians, in addition to steroid receptor-positivity, by an age peak incidence of about 74 years, and the group of "basal and HER2-expressing receptor-negative tumors with a significantly different peak at the age of 50–52 years. Ethnicity turned out to be an important factor modifying both the receptor phenotype of breast cancer tissue and the frequency of detection of individual subtypes of the disease, which is seen, in particular, in the Japanese and African American populations [5].

In a later work, A. Kurian et al. (2010) confirmed that the peak detection of luminal neoplasms occurs in women over the age of 70 years (about 32–35% of tumors of this kind versus 20–23% at the age of 50–59 and 60–69 years). HER2 and TH carcinomas, as noted earlier, were characterized by a peak in the range of 40–59 years. Such a repeatedly attested "binding" to the stages of oncogenesis, characterized, in particular, by lower or higher estrogen saturation, allows us to refer to the information that describes the state of the reproductive function of patients with various subtypes of breast cancer based on anamnestic and epidemiological data. Despite variability (by ethnicity and age), it appears that the risk of developing luminal carcinomas (both A and B) is increased in women who have not had a childbirth, as well as with the onset of menopause over the age of 53–55 years, and may decrease with prolonged feeding, exceeding 6 months. The arrival of menarche earlier than 13 years was associated with cases of breast cancer characterized by overexpression of HER2+, but unlike the previously expressed point of view, it did not increase, but reduced the risk of TN (basal cell) carcinomas. With the same TN breast cancer, the absence of childbirth in history does not affect the degree of risk. Age at first birth over 30 years has recently been shown to be little associated with risk of luminal or TN neoplasms, but increases the risk of developing HER2+ breast cancer. That is, it is possible that non-luminal variants of the disease also have a certain hormone sensitivity and dependence on the hormonal metabolic status [6].

Recently, gene expression in breast cancer has been actively studied all over the world by DNA microanalysis methods. The results of these studies are applicable to determining the prognosis for breast cancer, predicting the effect of therapy, and even classifying breast cancer according to genome features. So S.M. Perou distinguishes 5 types of breast cancer according to the features of gene expression: luminal (subtypes A and B), basal, type HER2+, a group with the expression of a "normal" gene profile.

This classification has clinical implications: the basal and HER2+ types have the worst prognosis, while the luminal type has a high survival rate.

Based on the above data, it was proposed to determine several molecular genetic forms of breast cancer.

1. Breast cancer corresponding to the level of breast stem cells. The "cloudin" genes of the family are "disabled". This form occurs in 5-10% of patients, more often at a young age. It is determined by the following characteristics: the genetic profile of the tumor is similar to the profile of breast stem cells. Often revealed: lymphocytic infiltration, ER–, PR–, HER2–, Grade III. This form is distinguished by relatively lower chemosensitivity, lack of effect after the use of targeted drugs, poor prognosis. Aggressive treatment is needed.

2. Breast cancer corresponding to the level of a bipotent and early luminal precursor (BRCA1 - mutated or its expression is sharply reduced); base variant. This form occurs in 10-25% of patients, more often at a young age. It is determined by the following characteristics: ER–, PR–, HER2–, Grade III, sometimes with expression of steroid hormone receptors, Cut 5/6 – 60%, EGFR – in 50–70% of cases. Histologically - invasive ductal or (rarely) lobular carcinoma, metaplastic carcinoma, oat cell carcinoma. The form is characterized by a special genetic profile, an unfavorable prognosis. Metastases are often found in the visceral organs and the brain. However, with this form, a relatively high chemosensitivity of the tumor was noted. The administration of platinum preparations, PARP inhibitors, angiogenesis inhibitors, dose intensive therapy is effective. The rapid development of chemoresistance was noted. This form requires aggressive treatment.
3. Breast cancer corresponding to the level of the late luminal precursor. HER2+ variant. This form occurs in 10-15% of patients, from young age to menopause. It is determined by the following characteristics: ER–, PR–, HER2+, Grade, in 1/3 of patients overexpression of Toro2a is detected. The form is characterized by an unfavorable prognosis. Metastases are often found in the visceral organs and the brain. With this form, a high chemosensitivity of the tumor was noted. High efficiency of adjuvant and neoadjuvant chemotherapy (CT) with the appointment of trastuzumab (an anti-HER2 monoclonal antibody) and lapatinib (an inhibitor of HER1 and HER2 tyrosine kinase). This form requires aggressive treatment.
4. Breast cancer (luminal B), corresponding to the level of differentiated cells. The form occurs in 10-15% of patients. They are detected in young, perimenopausal and early postmenopausal age. Characteristics: ER±, PR±, HER2±, Grade II−III; possible overexpression of Toro2a, in combination with overexpression of HER2. The form is characterized by an unfavorable prognosis. Metastases to visceral organs, brain, bones and soft tissues, skin, lymph nodes (LN) are often detected. High chemosensitivity of the tumor was noted to anthracyclines (with overexpression of Toro2a), taxanes, and other drugs.

The basal type is most common in premenopausal African American women (39%) compared to postmenopausal African American (14%) and non-African (16%) women in this population. As you know, tumors in this type of breast cancer grow and spread faster and more often lead to a fatal outcome than others. The high prevalence of the basal-like type and the slightly lower prevalence of the luminal A-type partly explain the higher mortality among young African-American women with breast cancer.

In general, African American women have a lower risk of breast cancer than white women, but the mortality rate from this disease, on the contrary, is significantly higher. The key to explaining this phenomenon is the fact that African American women are more likely to be diagnosed with breast cancer that does not contain estrogen receptors, progesterone and HER2 (breast cancer with a TH phenotype). Such breast cancer flows extremely aggressively and is insensitive to targeted and biological systemic therapy, including hormone therapy and herceptin. In 2010, 2 studies examined breast cancer in West African women, who can be considered modern African-American women due to the hypothesis of their common origin.

The first study of its kind examined the distribution of molecular subtypes of invasive breast cancer in native West African women by evaluating 507 slides of tumors from women born in Nigeria and Senegal. It was found that in approximately 75% of cases, breast cancer did not express hormone receptors, and more than 50% of patients had a basal or unclassified TH subtype.

In another study, a high risk of breast cancer with a TH phenotype was concluded based on

the analysis of women of African American origin (n = 581), 1008 white American women and 75 patients from Ghana with breast cancer. The highest frequency of breast cancer with TH phenotype was found in women from Ghana (82%), the lowest - in white American women (16%); in African American women, the frequency was intermediate - 26%. Similar data were obtained for breast cancer that does not express estrogen receptors: its proportion was 76% in women from Ghana, 36% in African American women and 22% in white American women [7–9].

Despite the high results of treatment, in 20–30% of patients with early breast cancer, the disease progresses with the development of distant metastases. The likelihood of progression depends on the stage of the disease at the time of diagnosis and the biological characteristics of breast cancer. Independent risk factors for recurrence include tumor size, lymph node involvement, grade of malignancy, lymph node and blood vessel invasion, estrogen receptor status, and human epidermal growth factor 2 (HER2) status. However, the nature of distant metastasis is not well understood. The process of metastasis occurs according to the classical scheme: tumor ingrowth into blood vessels, release of tumor cells into the bloodstream, extravasation, proliferation, angiogenesis, and microenvironment of the target tissue. Metastases usually retain the characteristics of the primary tumor. Described certain gene sequences associated with metastasis to the lungs and bones, as well as the relationship of the expression of HER2 and estrogen receptors with an increased risk of metastasis to certain organs. And only a few studies show the nature of metastasis of one or another of the main biological subtypes of breast cancer, isolated by gene expression or immunohistochemical markers.

In the study, distant metastases were defined as disease recurrence beyond the ipsilateral breast, chest wall, or regional lymph nodes. Organs with distant metastases were divided into the following categories: brain (including ventricular choroid plexuses, central nervous system, pituitary, meninges, and frontal sinus), liver, lungs (including cancerous lymphangitis), bones (including bone marrow), distant lymph nodes (other than ipsilateral axillary, supraclavicular, or internal mammary), pleura or peritoneum (including ascites, omental involvement, pleural effusion, and peritoneal carcinomatosis), others (including skin outside the breast and chest wall, ovaries, spinal cord, eyes, heart, organs other than listed) and unknown (distant metastases are present, but the localization is not specified).

According to D.A. Karseladze (2010), who studied patients with TN in the period 1996-2008. (n = 88), revealed the following patterns: it usually occurs in the age range of 41–60 years, clinically predominantly BC stage I–II (60.2%), a tendency to early extensive hematogenous metastasis, including in the brain (4, 6%). Patients with TN breast cancer have a more burdened family and hereditary oncological anamnesis, both on the maternal and paternal lines. With TN breast cancer, 12.5% of patients develop bilateral breast cancer, more often metachronous. TNF is detected in all second tumors, both synchronous and metachronous, developing 10–16 years after the removal of the first neoplasm. From the standpoint of traditional histological classification schemes, TN breast cancer is a heterogeneous group of tumors represented by a wide variety of microscopic structures - from ductal to medullary cancer with lymphoid stroma. Most of these tumors have a high histological grade (75.7%) [10].

According to L.K. Choi et al. (2010), who analyzed the data of 51 patients with breast cancer (stage I - n = 10; stage IIa - n = 41), the frequency of occurrence of various molecular subtypes in the study group varied (observation period 2005−2010) [11].

According to D.D. Paka (2012), in the 1st place, the percentage of recurrence after organ-preserving operations on the breast in the HER2 subtype of breast cancer and it was 10%, in the 2nd place - in case of TN breast cancer - 6.1%, in the 3rd place - luminal And the subtype is 4.7% [12].

Thus, the division of breast cancer into subtypes is, first of all, a search for features of recurrence and distant metastasis, as well as an analysis of the possibilities of different approaches to the treatment of such a heterogeneous disease. Undoubtedly, scientific research will continue, since the treatment of this disease is very important both socially and economically.

References:

1. Malignant neoplasms in Russia in 2010 (morbidity and mortality). Ed. IN AND. Chissova, V.V. Starinsky, G.V. Petrova M., 2012. 260 p.
2. Pak D.D., Rasskazova E.A., Ermoshchenkova M.V. Mammary cancer. M., 2010. 160 p.
3. Kris M.G., Benowitz S.I., Adams S. Progress in clinical oncology 2010: the most significant advances in the treatment, prevention and screening of cancer. Report from the American Society of Clinical Oncology (ASCO). Zhurn klin onkol 2011;5(1):80−101.
4. Pak D.D., Rasskazova E.A. Organ-sparing treatment of breast cancer. M., 2012. 191 p.
5. Anderson W.F., Pfeiffer R.M., Dores G.M., Sherman M.E. Comparison of age distribution patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15(10): 1899-905.
6. Kurian A.W., Fish K., Shema S.J., Clarke C.A. Lifetime risks of specific breast cancer subtypes among women in for racial/ethnic groups. Breast Cancer Res 2010; 12(6):99.
7. Kennecke H., Yerushalmi R., Woods R. Metostatic behavior of breast cancer subtypes. J Clin Oncol 2010; 28(20):3271-7.
8. Taneja P., Maglic D., Kai F. et al. Classical and prognostic markers for breast cancer and their clinical significance. Clin Med INS Oncol 2010; 4:17-34.
9. Letyagin V.P. Present and future of anti-Her-2 therapy for breast cancer. OECD 2011; 2:41-4.
10. Karseladze D.A. Triple negative breast cancer (clinical and biological features). Abstract dis. … cand. Honey. Sciences. M., 2010. 25 p.
11. Tsoi L.K., Bogatyrev V.N., Vysotskaya I.V. Cytofluorometric characteristics of molecular subtypes of breast cancer. OECD 2010; 4:40−2.
12. Pak D.D., Rasskazova E.A. Recurrence of breast cancer after organ-preserving treatment. Oncosurgeon 2012; 4(2):37−49.