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Retrospective Review on Breast Cancer Patients to Assess Molecular Classification

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Abstract: *Breast cancer is a heterogeneous group of tumors that differ in morphology, clinical course and sensitivity to treatment. The classification of breast tumors published by WHO includes numerous histological forms. The majority of breast cancer is represented by invasive protocol cancer, without additional clarifications and is about 50 - 80%. Based on the immuno-histochemical study of the expression of breast carcinoma of the chest receptors for estrogen and progesterone (ER, PR) and receptor of the epidermal growth factor of the second type (HER2/neu, ErbB2), BC is classified into 4 molecular subtypes. These subtypes differ among themselves according to the prognosis of the course and the response to medical therapy. In general, the luminal, HER2 + and triple negative (TH) molecular subtypes of the breast cancer are distinguished. According to modern concepts, patients with hormone-sensitive tumors, positive for estrogen receptor (ER) and / or progesterone (PgR) receptors, are clearly distinguished by their biological characteristics. These tumors are characterized by the presence of Her-2 / neu hyper expression, and patients with so-called triple negative tumors that are negative in both ER and / or PgR content and Her-2 / neu content. Current retrospective review aims to assess the molecular classification of breast cancer.*

Keywords: *Breast Cancer, Luminal A, Luminal B, Basal-like, triple negative, molecular classification.*

1. Introduction

Breast cancer (BC) is referred to be as a heterogeneous disorder consists of manifold subcategories of several cellular compositions, molecular alterations, and clinical behavior. Breast cancer is one of the most common cancer across the world [1]. According to the records of World Health Organization, the standardized incidence rate of the breast cancer in 2013 is 60.5 cases per 100,000 women. Although the incidence of malignant tumors of the mammary glands is constantly increasing, mortality from them tends to decrease. The breast cancer is a heterogeneous group of tumors that differ in morphology, clinical course and sensitivity to treatment. However, even histologically similar tumors have a different natural history, which is due to a certain limited morphological classification of the breast cancer. Examination of gene expression by the breast cancer cells and their correlation with phenotypic manifestations made it possible to identify a number of biological subtypes of the breast cancer [2]. These examinations determine the natural history, clinical, pathological and molecular properties of the tumor, and are key factors prejudging the prognosis of the course and effectiveness of systemic drug therapy.

The problem of the morphological heterogeneity of breast cancer has long been recognized by histopathologists, who have made many years of efforts to develop classification systems that take into account the diversity of this cancer. The classification of breast tumors published by WHO includes numerous histological forms. The majority of breast cancer is represented by invasive protocol cancer, without additional clarifications and is about 50 - 80% [3]. Correlation between immune-histochemical markers and tumor sensitivity to drug treatment is well studied and underlies clinical recommendations on adjuvant treatment of the breast cancer. However, the number of studies evaluating the relationship between molecular subtypes and the clinical and biological characteristics of the breast cancer is limited. The use of protracted and expensive methods of genetic analysis in everyday clinical practice is impossible. However, the research on the correlation between gene expression and immuno-histochemical markers in a tumor has made it possible to identify a number of molecular subtypes of the breast cancer, which can be determined in routine clinical practice. This research aims to formulate a retrospective review based on the molecular classification of breast cancer.

2. Literature Review

Breast cancer (BC) is the most commonly diagnosed female cancer [5]. BC ranks first in Saudi females as well, accounting for 26% of all newly diagnosed female cancers as reported by the National Cancer Registry, Saudi Arabia [6]. In the US and Western Europe, the median age at presentation is ~63 years in comparison to 48 years in Saudi Arabia [6]. Over the years, oncologists have attempted to classify breast tumors, seeking for a physical similarity to discover common biological mechanisms. Attempts to group breast cancer around clinical and pathological parameters were unconvincing [4]. It was initially proposed to divide all carcinomas into luminal and basal, depending on the cyto-keratins are expressed. The markers are designated by the name of the layers of the normal epithelium of the breast. There is also a strong association between early relapses of breast cancer and the expression of basal cyto-keratins.

However, the basal BC is usually estrogen-negative, low-differentiated and have a poor prognosis. The use of the microchip technique for total screening of the transcriptional activity of the cancer cell genome allowed to reach a new level in understanding the causes of the phenotypic heterogeneity of breast tumors. In the early 2000, the microchips containing hybridization probes to 8102 mRNA were also assessed to attain individual expression profiles of tumors [5].

The use of cluster analysis made it possible to isolate the inner panel of 465 genes that coordinated between the samples, determining five different expression patterns. In accordance with these patterns, all carcinomas were divided into several molecular subtypes. The first two groups present the positive status of estrogen receptors (ER) related to the luminal subtypes A and B. However, a group expresses HER2 receptors in excess and in the last group, expression of breast genes remains normal, and basal or thrice-negative tumors. Subsequently, the existence of these molecular subtypes has been repeatedly confirmed in independent studies. Moreover, it turned out that the pattern of expression remains similar in the primary and metastatic tumors, even if the latter develops several years later. RNA profiling by carcinoma in situ, also demonstrated the validity of this molecular classification.

Molecular Classification of Breast Cancer

Different studies have revealed different classifications of breast cancer on the basis of distinct grounds. For instance, the types of breast cancer may be presented according to the grades and stages of tumor. The determination of the molecular types of the breast cancer on the basis of immuno-histochemical evaluation of the expression ER, PR and Her2 / neu is inexpensive and sufficiently informative, but at the same time a simplified diagnostic method [8]. It is worth discussing to highlight the significance of the introduction of new markers, the molecular classification undergoes changes, which makes it possible to increase its predictive reliability.

Based on the immuno-histochemical study of the expression of breast carcinoma of the chest receptors for estrogen and progesterone (ER, PR) and receptor of the epidermal growth factor of the second type (HER2/neu, ErbB2), BC is classified into 4 molecular subtypes. These subtypes differ among themselves according to the prognosis of the course and the response to medical therapy [9]. Molecular subtypes of the breast cancer, which are of fundamental clinical importance, are listed in Table 1. In general, the luminal, HER2 + and triple negative (TH) molecular subtypes of the breast cancer are distinguished.

Molecular subtype	**Immuno-histochemical portrait**			**Frequency of detection**
	ER	**PR**	**HER2 / neu**	
Luminal A	+	+	-	56 – 61 %
Luminal B	+	+	+	9 – 16 %
HER2 +	-	-	+	8 – 16 %
Basal-like / Triple negative	-	-	-	8 – 20 %

Table 1: Immuno-histochemical phenotype of molecular subtypes of the breast cancer

About 25% of invasive breast cancer is represented by other special histological forms [10] Tumors of this group are not always recognized by histological examination and can be mistakenly assigned to the invasive protocol cancer group. In the present system of histological classification, the criteria for determining the degree of breast cancer are fairly subjective, the results of the study are not always reproducible by different patho-morphologists. In addition, the classification does not reflect intra-tumor heterogeneity and the biological complexity of breast tumors. Currently, only the morphological verification of the pathological process, as a malignant neoplasm, is insufficient for an individual prognosis of breast cancer. Today, research in biochemistry and molecular biology opens new avenues for the diagnosis and therapy of breast cancer. The determination of molecular-biological markers (MBM) in tumor tissue can provide additional information on the rate of its growth, the ability to metastasize, and resistance to chemotherapy drugs [12]. Characterizing the biological characteristics of each specific tumor, they can help in predicting outcomes of the disease and in individualization of treatment. On the basis of gene expression using microarray technology, revealed several subtypes of BC: luminal type (A and B), basal type, type HER2 + / ER-, type with normal gene expression. The number of indicators considered as potential MBM for breast cancer, is rapidly increasing, reflecting the achievements in the study of mechanisms for the regulation of proliferation and differentiation of tumor cells.

Luminal tumor A

1. Cluster of genes highly expressed in Luminal A tumors: “estrogen receptor (ESR1), XBP1, FOXA1, GATA3, TTF3, LIV3, HER4, PIK3RI, luminal cytokeratins (KRT8 / 18). IHC markers: ER / PR +, HER2-, KRT8 / 18 +”.
2. Activated pathways and processes: ER signaling pathway, fatty acid metabolism.
3. Clinical-pathological and prognostic features: estrogen-dependent tumors; characterized by a later age at the time of diagnosis, a high degree of differentiation, a low proliferative index.

“Luminal-like tumor” expresses hormone receptor with an expression profile evocative to the luminal epithelial constituent of breasts [13]. In other words, the tumors that express receptors for ER and PR are luminal. Depending on the expression of HER2 / neu, these luminal tumors are classified into A (that do not express Her2 / neu) and B (that express Her2 / neu). It has been established that luminal types are associated with less aggressive flow and a good prognosis in comparison with HER2 + and TN of the breast cancer. For example, with a high mitotic activity of cells (Ki-67> 14%) tumors with a luminal A phenotype, according to the recommendations of the St. Gallen Congress on the treatment of the breast cancer (2011), are assigned to the luminal B Her2 / neu-negative molecular subtype [14]. The need to isolate the luminal B Her2 / neu-negative type of the WPH is dictated by the natural history of these tumors, which is more

similar to the natural history of luminal B than luminal A tumors.

Tumors of this type are less aggressive, characterized by better prognosis than receptor-negative cancers. These patients have shown a significant reduction in the risk of relapse within the first 2 years; increased overall survival. High efficacy of hormone therapy (tamoxifen and aromatase inhibitors) and neoadjuvant chemotherapy (doxirubicin, paclitaxel). There is a significant number of BRCA2-associated cancers are of this type.

Luminal tumor B

1. A cluster of genes highly expressed in tumors: "ESR1, CCNB1, MKI67 (Ki-67), MYBL, CCNE1, ERBB2, GRB7, HRAS. IHC markers: ER / PR +; HER +; Ki-67> 13%".
2. Activated pathways and processes: HER2 signaling pathway, proliferation.
3. Clinical-pathological and prognostic features: estrogen-dependent aggressive tumors; characterized by early diagnosis, low differentiation, high proliferative index, large tumor size, involvement of lymph nodes.

Tumors of this type have a significantly worse prognosis and a greater likelihood of recurrence than other receptor-positive tumors [13, 14]. They are often not sensitive to tamoxifen and aromatase inhibitors, but are susceptible to trastuzumab. Molecular genetic features: amplification of the oncogene HER2 and 17q amplicon genes. There is a hyper-activation of key promoters of the cell cycle (e.g. cyclin E1) and cell growth (e.g. TOPOII). It represents the highest total level of methylation of the genome among all subtypes; genes RASSF1, GSTP1, CHI3L2 are specifically methylated. Cyclin E1) and cell growth (eg, TOPOII). The highest total level of methylation of the genome among all subtypes; genes "RASSF1, GSTP1, CHI3L2" are specifically methylated. Cyclin E1) and cell growth (eg, TOPOII) [17]. The highest total level of methylation of the genome among all subtypes are; "genes RASSF1, GSTP1, CHI3L2" are specifically methylated.

HER2 +

1. A cluster of genes highly expressed in tumors: "ERBB2 (HER2), GRB7, HRAS, MEK1 / MEK2, AKT1. IHC markers: ER- / PR-; HER2 +; Ki-67> 13%".
2. Activated pathways and processes: "EGFR / HER2 signaling pathway, proliferation".
3. Clinical-pathological and prognostic features: estrogen-independent aggressive tumors with a high proliferative index.
4. Characterized by low differentiation, a larger tumor size, involvement of lymph nodes.
5. Effectively adjuvant trastuzumab administration; are not sensitive to hormone therapy.

HER2 + are tumors with overexpression of Ne2 / neu and the absence of ER and PR. So far, discussions are under way about which gene panel should be used for the most accurate classification of tumors, how homogeneous the described subtypes, and whether it is necessary to isolate additional groups [18]. The frequency of the HER 2 subtype is independent of race, or of menopausal status. If the genetic risks of HER 2 are considered, it turns out that such popular low-prone genes of predisposition as "FGFR2, TNRC9, 8q24, 2q35 and 5p12" contribute significantly to the development of estrogen-positive variants of breast cancer, but not estrogenegative. The vast majority of BRCA1-associated cancers are thrice-negative; the expression profiles of such carcinomas are similar to those of basal BC. In contrast, carriers of BRCA2 mutations often develop luminal A and B tumors. The described regularity extends to carcinomas in situ. The combination of these data strongly suggests that estrogen-positive luminal, estrogen-negative basal breast cancer and HER2-positive breast cancer are certainly different diseases, with different etiology and molecular pathogenesis [19].

An important circumstance is that the factors of the organism, both genetic and physiological, play a primary role in the choice of the pathway of molecular pathogenesis of this tumor. The combination of these data strongly suggests that estrogen-positive luminal, estrogen-negative basal breast cancer, and HER 2 – positive breast cancer are certainly different diseases, with different etiology and molecular pathogenesis. An important circumstance is that the factors of the organism, both genetic and physiological, play a primary role in the choice of the pathway of molecular pathogenesis of the tumor [20]. The combination of these data strongly suggests that estrogen-positive luminal, estrogen-negative basal breast cancer and HER 2 - positive breast cancer are certainly different diseases, with different etiology and molecular pathogenesis.

Basal-like or Triple Negative

1. Cluster of genes highly expressed in tumors: "oncogenes NRAS, KRAS, C-KIT, cadherin P (CDH3), laminin alpha / gamma (LAMA5, LAMC1), MCM3 / 4/7, basal cytokeratins (KRT5 / 6/17). IHC markers: ER- / PR-; HER2-; CK5 / 6 +, EFGR (HER1) +, cadherin-P +; vimentin +; c-kit +".
2. Activated pathways and processes: "p21, p53, FAS signaling pathways, protein phosphorylation, cell cycle stimulation and proliferation, dedifferentiation".
3. Clinical-pathological and prognostic features: estrogen-independent aggressive tumors.
4. Early diagnosis, protocol or metaplastic histological type, low differentiation, high proliferative index, large tumor size, involvement of lymph nodes, nuclear pleomorphism, necrosis, stromal lymphatic response are characteristic.

Tumors that are negative for the 3 above mentioned signs refer to the TN (basal-like) breast cancer. The TN subtype is associated with a high frequency of *BRCA1* mutation , aggressive course, a lack of response to hormone therapy and trastuzumab, low overall and disease-free survival [21]. Basal tumors are characterized by high aggressiveness, a high probability of development of locally distributed and metastatic forms. Patients with basal breast cancer have very poor prospects for recovery, regardless of the lesion of the lymph nodes. Survival in this group is lower than for any other molecular subtype, including HER 2 positive [22]. Despite the depressing prognosis, thrice-negative tumors are sensitive to standard chemotherapeutic regimens, including anthracycline. Its molecular genetic features include high frequency of somatic p53 mutations,

high level of genomic instability, PTEN aberrations, increased expression of telomerase, and inactivation of RB.

3. Methodology

The current study involves quantitative research methodology. The research methods involves data analysis of patient's information. It will assess the frequency of molecular classes of breast cancer from the retreived data.

Study Population

Approximately 740 patients were screened for breast cancer. Their data was retrieved from a local hospital located in Saudi Arabia.

Data Analysis

The data was analyzed through "Statistical Package for the Social Sciences" (SPSS). The data was segregated into sociodemographics, type of tumor, size of tumor, and overall survival rates.

4. Results

The results revealed that a total of 721 patients out of 740 were females, while 19 were males (Table 2).

Table 2: Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	721	97.4	97.4	97.4
	Male	19	2.6	2.6	100.0
	Total	740	100.0	100.0	

Furthermore, it was also assessed that around 391 patients were aged less than 50 years, while 349 were aged more than 50 years (Table 3).

Table 3: Age

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<50	391	52.8	52.8	52.8
	>50	349	47.2	47.2	100.0
	Total	740	100.0	100.0	

The size of tumor among the patients was also measured. It was found that 235 patients had tumor of 0.1 to 3 cm, while 425 patients presented the tumor of 3 to 6 cm. However, 80 patients had tumor greater than 7 cm (Table 4).

Table 4: Size

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0-3	235	31.8	31.8	31.8
	3-6	425	57.4	57.4	89.2
	>7	80	10.8	10.8	100.0
	Total	740	100.0	100.0	

While evaluating the histo-pathological type of tumor, it was observed that 634 patients had invasive ductal tumor, whereas 106 had other type of tumor (Table 5).

Table 5: Histo-pathological type

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Inasive Ductal	634	85.7	85.7	85.7
	Others	106	14.3	14.3	100.0
	Total	740	100.0	100.0	

The assessment of survival rates indicated that 78 individuals were dead during the treatment, whereas 662 patients remained alive (Table 6).

Table 6: Survival Status

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Death	78	10.5	10.5	10.5
	Alive	662	89.5	89.5	100.0
	Total	740	100.0	100.0	

5. Discussion

Molecular Genetic Analysis

On the basis of molecular genetic analysis, several biological subtypes of breast cancer have been identified, including luminal A, luminal B, HER2-positive and basal-like (including three times negative: TN cancer). In clinical practice, surrogate clinical and morphological criteria, including immunohistochemical determination of estrogen and progesterone receptors, overexpression and / or amplification of HER2, Ki-67 or the degree of tumor malignancy (G), are used to identify the biological subtypes of breast cancer [23]. Biological subtypes differ in biological flow and sensitivity to different types of systemic treatment, which requires different therapeutic tactics.

On the foundation of clinical grounds, different studies have revealed different types of breast cancer. There are several clinical forms of breast cancer, such as diffuse, edematous-infiltrative, Paget's disease, nodular cancer. Nodular cancer occurs most often in around 75 – 80 % of the cases [24]. The clinical manifestation of this form is the presence of nodal formation in the affected area of the breast. The uppermost quadrant is most often affected (up to 50 %). Approximately 90 % of cases reveal changes in the mammary gland themselves. The clinical picture of breast cancer is diverse and primarily depends on the stage of the disease and the clinical form of the tumor. A timely mammography can reveal non-palpable preclinical forms of cancer, when the only sign of a tumor process is a change in the radiographic pattern, rather than a palpable formation. The growth rate of a cancer tumor is precisely variable.

Molecular Classes & Detection of Breast Cancer

Different molecular types of breast cancer may be detected according to the clinical signs of the disease. Clinical signs of early forms of nodular breast cancer include the presence of tumor node in mammary gland, dense consistency of the tumor, limited mobility, painlessness, and presence of a single node in the armpit on side of the lesion. In some cases, there is a presence of skin symptoms, which

may include skin retention above the tumor that is determined by assessing the skin [25]. The peculiarities of the course and possible treatment of BC are primarily determined by the biological characteristics of tumor cells. It is determined by the content of steroid hormone receptors, Her-2 status, and the degree of malignancy, the prevalence of the process (stage of the disease), age and condition of the ovarian function of the patient. Clinical signs of late forms of breast cancer may involve a noticeable deformation of the skin of the breast in the place of the detected tumor (especially when viewed with hands up) and determined retraction of the skin over the tumor [26].

Sometimes, the patient also presents skin sprouting by a tumor or ulceration, thickening of the nipple and folds of the areola (Krause symptom), retraction, fixation of the nipple, deformation of the breast, decrease or increase in size, and soldered metastatic lymph nodes in the armpit. Moreover, there is a supraclavicular metastases from the same side or cross axillary and supraclavicular metastases from the opposite side. The distant metastases are detected clinically or radiological. Furthermore, the diffused forms of cancer are mastoid, edematous-infiltrative, and armored forms. These forms are found mainly in young women and are highly malignant. In addition, Paget's disease occurs in 5 % of all cases of breast cancer [27]. It begins with the appearance of dry and wet crusts, reddening, and thickening of the nipple. The process can be extended to the areola. Gradually, the nipple flattened, ulcerated, the process spreads to the skin of the breast beyond the areola. Simultaneously, the process spreads through large ducts deep into the breast. At the beginning of the disease, the disease may resemble eczema. Later, metastases appear in the regional lymph nodes.

Incidence of Breast Cancer & Hormonal Factors

Scientists have investigated the incidence of breast cancer of four tumor subtypes, which are determined by several hormonal factors [28]. Using this data, the researchers determined that the frequency of each subtype of breast cancer depends on a number of factors. For example, the less aggressive subtype of breast cancer, HR + / HER 2-, is widespread among white women. Analyzing the results by age, the researchers found that HR + / HER2- occurs in women over the age of 45 and is more common in the white race of non-Latin American women than in members of other groups. The results found that the most aggressive subtype of breast cancer, HR- / HER2-, is widespread among women. They have the highest percentage of breast cancer diagnosis in the late stages of all subtypes. These parameters associated with low survival rates of breast cancer and explain why women have high rates of mortality from breast cancer.

Clinical Trends and Molecular Classification

Statistical data of recent years indicate an increasing rate of breast cancer incidence and is characterized by a great variety of clinical trends. These trends range from aggressive with rapid growth, early and multiple metastasis to relatively benign, with slow growth and late and rare metastasis. Moreover, invasive breast cancer is a heterogeneous group of tumors with a wide variation in clinical manifestations, prognosis and morphological spectrum [29].

Among tumors with positive immunohistochemical staining for estrogen and progesterone receptors, only 73% are classified as luminal A and B tumors by RNA profiling. 11 % are HER2-positive, 5% - basal and 12% -normal expression subtype. In contrast, among ER-negative carcinomas, about 11% are in luminal A or B by expression data [30]. Among HER2-positive tumors, 6% are basal, while almost 9% of cases with negative staining for HER2 turn out to be a HER2 subtype according to expression data. The use of additional myoepithelial markers and the analysis of the proliferation index help to minimize the percentage of errors and achieve high accuracy of classification. At least, the most clinically relevant groups, i.e. basal and HER2, can be identified with great accuracy. To date, the use of a panel of the following surrogate immuno-histochemical markers is recognized as the gold standard: "ER, PR, HER2, Ki-67, CK5 / 6, EGFR or vimentin (VIM)". While labeling the tumor immunophenotype, one often has to deal with the heterogeneity of the tumor by staining it with basal and luminal markers.

In this connection, there is an allocation of a special heterogeneous or basic type. In this case it is obvious that different populations of tumor cells have different biology and will specifically respond to the therapeutic effect. Note that this heterogeneity remains outside the expression approach, since in the latter case, the total and RNA from the totality of all tumor cells are analyzed.

Hormone-Sensitive Tumors

According to modern concepts, patients with hormone-sensitive tumors, positive for estrogen receptor (ER) and / or progesterone (PgR) receptors, are clearly distinguished by their biological characteristics. These tumors are characterized by the presence of Her-2 / neu hyper expression, and patients with so-called triple negative tumors that are negative in both ER and / or PgR content and Her-2 / neu content. These clinical groups correspond to molecular subtypes of breast cancer, determined by the expression profile of various genes, including luminal A and B, Her-2 / neu positive and basal-like. Hormone-sensitive BC can be luminal A, which is positive for ER and / or PgR without the overexpression of Her-2 / neu. However, the luminal B, in which the tumor is positive both in the content of ER and / or PgR, and in Her-2 / neu content. Therefore, subtype B is characterized by a greater proliferation activity than in subtype A, a risk of recurrence and metastasis, but at the same time a greater susceptibility to cytostatics [30]. The disease prognosis is most favorable in patients with hormone-sensitive tumors, in which case it is possible to count on the effect of hormone therapy as the least toxic and relatively effective method of treatment in this category of patients.

Epidemiological Association

Furthermore, the data from epidemiological studies show, that risk factors may vary depending on the molecular subtype. Tumors of the luminal type A are most common; they are characterized by risk factors that have traditionally indicated earlier for breast cancer. Opposite situation is observed for basal carcinomas [31]. Especially high risk of basal cancer in elder women who have not breast-fed, and women who have been through a drug interruption of lactation. Tumors of the luminal type A, as a rule, occur at a

later age than the other groups; and basal in the earlier age. It is also known that the basal type of breast cancer is much more likely to occur in young women than in elder women.

6. Ethical consideration

Ethical considerations have been properly followed while formulating this retrospective review. No personal information of any patient has been disclosed. Appropriate approval was taken by the Institutional Review Board.

7. Conclusion

Breast cancer is the most common malignant tumor among the female population across the world. Despite the fact that many researches have been devoted to its pathogenesis, early diagnosis and development of new methods of treatment; it continues to be a topical problem of oncology and medicine in general. Analysis of the etiological and molecular heterogeneity of breast cancer serves as a basis for a better understanding of the mechanisms of carcinogenesis and tumor progression. However, dynamic discussions around the molecular taxonomy of breast cancer are aimed at developing the descriptive aspect of this classification, but rather in optimally implementing the achievements of molecular taxonomy in the standards of treatment of patients. While deciding on the choice of therapy, the clinician progressively needs information about the molecular-biological characteristics of the tumor the properties of the cancer cell genome, the work of repair systems, apoptosis, and activation of signaling cascades. Thus, molecular classification and analysis of expression patterns becomes a powerful tool for individualizing therapy and predicting its effectiveness.

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9. Conflict of interest

No conflict of interest has been declared by the researchers.

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