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FEATURES OF BREAST CANCER IN PATIENTS OF YOUNG AGE: SEARCH FOR DIAGNOSIS OPTIMIZATION AND PERSONALIZED TREATMENT

The statistical data of the recent decades demonstrate a rapid growth of breast cancer (BCa) incidence and a tendency toward its increase especially in young women. In the structure of morbidity of women in the age group of 18—29 years, BCa ranks first and in the age range of 15—39 years, BCa is one of the leading causes of mortality. According to the data of the epidemiological and clinical studies, the young age is an independent unfavorable prognostic factor of BCa that is associated with an unfavorable prognosis and low survival rates and is considered an important predictor of the disease aggressiveness, a high risk of metastasis and recurrence. The variability of clinicopathological and molecular-biological features of BCa in patients of different age groups as well as the varying course of the disease and different responses to the therapy are mediated by many factors. The analysis of the literature data on the factors and mechanisms of BCa initiation in patients of different age groups demonstrates that the pathogenesis of BCa depends not only on the molecular-genetic alterations but also on the metabolic disorders caused by the current social and household rhythm of life and nutrition peculiarities. All these factors affect both the general condition of the body and the formation of an aggressive microenvironment of the tumor lesion. The identified features of transcriptome and the differential gene expression give evidence of different regulations of the immune response and the metabolic processes in BCa patients of different age groups. Association between the high expression of the components of the stromal microenvironment and the inflammatory immune infiltrate as well as the increased vascularization of the tumor lesion has been found in BCa tissue of young patients. Proving the nature of the formation of the landscape comprising molecular-genetic, cytokine, and immune factors of the tumor microenvironment will undoubtedly contribute to our understanding of the mechanisms of tumor growth allowing for the development of algorithms for delineating the groups at high risk of tumor progression, which requires more careful monitoring and personalized treatment approach. This will be helpful in the development of innovative technologies for complex BCa treatment.

Keywords: breast cancer in young women, clinicopathological and molecular-biological features, tumor microenvironment.

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The analysis of the global and Ukrainian statistical indices of cancer morbidity and mortality has shown the rapid growth of breast cancer (BCa) incidence [1—5]. According to the expert data, the current stage of the anticancer struggle is characterized, on the one hand, by significant progress in optimizing diagnostics and increasing the effectiveness of cancer therapy, and, on the other hand, by a steady increase in the morbidity and the emergence of increasingly aggressive forms of cancer. According to Cancer Statistics, in 2020, against the background of all nosological forms of malignant neoplasms, BCa surpassed even the incidence of lung cancer and confidently leads the ranking of the leading causes of death from cancer [1].

BCa attracts attention due to the rapid increase in the amount of information on its etiological factors, the molecular genetic links of pathogenesis, and features of tumor cell biology. The studies of BCa have revealed a tendency toward an increase in its incidence in young and very young women with a simultaneous increase of more aggressive BCa phenotypes and a less favorable prognosis [1, 6].

According to the GLOBALCAN data, over the past 30 years, the percentage of newly diagnosed BCa among very young patients (up to 34 years old) has been increasing significantly [7—10]. As a result, in the structure of morbidity of women in the age group of 18—29 years BCa ranks first and in the age range of 15—39 years is one of the leading causes of mortality [2, 11]. An analysis of the data from a retrospective epidemiological study in seven European countries revealed that the average incidence rate of BCa in young women is increasing by 1.2% annually. In females of the age group from 15 to 34 years old, compared to older women (35—39 years old), the greatest increase was determined in all countries of the world, including the countries with a high level of socioeconomic prosperity [3, 12—14].

It is believed that the young age is an independent unfavorable prognostic factor of BCa. Therefore, BCa in young people is singled out as a separate task of molecular biological and clinical research. According to the WHO, the age of 25 to 44 years is considered young [15], while in the scientific literature, the definition of "young or very young women" varies from 35 to 40 years [16—18].

The main prerequisites for the in-depth study of BCa in young patients are the identification of the aggressiveness of its course in various molecular and biological subtypes. The young age of patients with BCa is associated with an unfavorable prognosis and low survival rates and is considered an important predictor of disease aggressiveness. Conducting new molecular biological studies, especially in younger patients, is dictated by the need to improve the results of screening, prevention, treatment, and diagnosis of cancer [19].

One of the first studies in this field was a retrospective analysis of the epidemiology of BCa in young people in a 25-year period conducted by the US National Cancer Institute, according to the data of which survival rates were lower in patients under 40 years compared to older women [20]. The lowest overall 5-year survival rate was found in women aged 25—29 years (72%), while similar survival rates for patients with BCa in the age categories of 30—34 years and 35–39 years were 76% and 80%, respectively. In contrast, the average overall 5-year survival rates of women with diagnosed BCa aged 45 to 80 years were higher and amounted to 84%—86% [19, 20].

A retrospective study of the open resource Registro de Cáncer de Mama of the Argentine Society of Mammologists conducted from January 2000 to January 2017 revealed significant clinicopathological differences between young (≤ 40 years) and very young (≤ 35 years) patients allowing the identification of a more aggressive BCa phenotype in the group of younger patients. The multivariate analysis showed that Her2/neu-positive phenotype, histological grade, and tumor size were independently associated with

younger age. Patients under 35 years of age, compared to patients aged 36 to 40 years, had a higher percentage of Her2/neu-positive tumors and progesterone receptor-negative neoplasms. Similar data on a more aggressive course of BCa with overexpression of Her2/neu associated with young age ≤ 35 are also confirmed by other clinical studies [21].

It has been proven that BCa in young patients is characterized by the aggressiveness of the disease course, high risk of metastasis, low sensitivity to chemotherapy, and rapid development of local recurrences, which is the main reason for the high mortality of women in this age group. In a comparative study of clinicopathological and molecular-biological features of BCa in patients of different age categories, it was found that in the group of patients of young age, the highest frequency of disseminated BCa with the presence of metastatic lesions of regional lymph nodes and distant organs was determined in comparison with patients older than 45 years [22].

The specified clinical and morphological features of BCa and the increased risk of its progression in young and very young women are increasingly being considered a separate direction in the study of the ways for special treatment. The increased health awareness, effective strategies for prevention and diagnosis, and improved access to treatment are extremely important for curbing the rapid development of BCa in the very young population [18].

Recently, an active search for a conventional denominator and the development of the virtual model systems have been carried out, which can allow inventorying, integrating, and synchronizing the results of the numerous studies on the identified individual molecular-genetic, clinicopathological, and epigenetic disorders in the development of BCa.

The analysis of the literature data on the factors and mechanisms of initiation of BCa among patients of different age groups has revealed the primary molecular-genetic hormonal disorders and the association with the features of the modern social and household rhythm of life and nutrition peculiarities. In particular, according to the data published on the American resource National Center for Health Statistics Data, the change in the food preferences of US residents in the period 1889—2009 is closely related to the increase in the number of overweight, obese, and extremely obese people [23]. Research by Kelly et al. [24] reported that the number of overweight people almost doubled from 1980 to 2008, and according to the current forecasts, this figure might reach 57.8% by 2030. At the same time, it was established that metabolic disorders affect both the general condition of the body and the formation of an aggressive microenvironment of the tumor lesion [25].

To date, it has been proven that insulin imbalance acts as a trigger for metabolic disorders that can inhibit apoptosis and increase the proliferation of tumor cells [26, 27]. A prospective cohort study found that high tumor aggressiveness and axillary lymph node involvement are associated with plasma insulin levels. Patients with high insulin levels have an increased risk of disease recurrence [28].

Simultaneously with the development of metabolic disorders, there are observed changes in the expression of steroid hormones, including estrogens as active promoters of carcinogenesis. An increase in the level of estrogen in the body, caused by obesity, is considered one of the mechanisms of BCa development [29]. Adipocytes increase the expression of pro-inflammatory factors, such as TNF-α, IL6, and many others, which, through the obesity-inflammation-aromatase axis, lead to the increased frequency of the *CYP19* gene transposition, which encodes aromatase, a key link in estrogen synthesis. The adipose tissue not only stores adipocytes but also is a recognized endocrine organ that produces biologically active molecules called adipokines. Adipokines bind to specific receptors on the sur-

face of target cells and affect the metabolism of tissues and organs. Among the adipokines, leptin increases disease risk, while adiponectin may have a protective effect. A number of researchers have shown that low levels of adiponectin are associated with an increased risk of BCa and its more aggressive phenotype. The obesity contributes to the remodeling of the extracellular matrix of the mammary gland by changing the function of adipocytes, stromal, endothelial, and immune cells. The interaction of these cells models the secretion of cytokines and estrogens and activates the endocrine-growth cascade of the tumor microenvironment [30].

An in-depth analysis of the molecular and biological characteristics of tumors in a young and very young group of patients revealed a number of genetic variants with low penetrance and rare genetic mutations with medium and high penetrance, including *BRCA1* and *BRCA2* gene mutations [31—35] that are indirectly involved in the BCa development regardless of the age. The loss of heterozygosity of the normal allele is often observed in tumors associated with *BRCA1/2* [36]. Other alleles of the high penetrance have been identified as a part of the inherited cancer syndromes. These include germline *TP53* mutations found in Li — Fraumeni cancer syndrome [37, 38], germline *PTEN* mutations in Cowden syndrome [39], and STK11/LK B1 mutations in Peutz — Jaeger syndrome [40]. However, all known genetic aberrations could not explain the development of BCa and its aggressive course in young patients.

A group of scientists, headed by Hatem A. Azim, established certain differences of selected genes at the transcriptional level depending on the age at BCa diagnosis [41]. For the first time, the differences in the somatic mutations and variations in the number of copies between young and elderly patients with BCa were determined and the expression of the corresponding genomic signatures at the mRNA level was evaluated. Eleven mutations were found to be independently associated with age at diagnosis, while only *GATA3* was associated with the occurrence of BCa in younger women. *GATA3* mutation was the main somatic event that characterized BCa arising only at a young age [41]. GATA3 is an important component of estrogen receptor signaling. Preclinical data indicate that *GATA3* mutations affect the binding of the estrogen receptor with DNA, modulate the response of BCa cells to estrogen signaling, may promote tumor growth and may be associated with endocrine resistance. This is extremely relevant, since the unfavorable prognosis associated with a younger age at diagnosis was mainly observed in patients with ER-positive BCa. It has been suggested that the higher prevalence of GATA3 mutations in these patients may cause higher resistance to endocrine therapy [42].

GATA-binding protein 3 (GATA3) is a member of a family of 6 GATA double zinc finger transcription factors (GATA1-6) that are required for mammary gland development and morphogenesis. The transcription factor GATA3 was first identified in the early 1990s and is considered a marker of luminal BCa subtypes [43]. GATA3 is involved in the differentiation and maintenance of ductal epithelium in the adult mammary gland, and mutations in the second zinc finger can affect DNA binding, indicating its critical role in the development and progression of BCa. *GATA3* was identified as one of the most significant mutated genes in BCa using whole-exome sequencing [44].

Later, during an in-depth study of molecular biological properties in the young and very young group, it was established that microRNAs, which can function as tumor suppressors and oncogenes, represent an important epigenetic factor in the regulation of GATA3 expression. In particular, it has been shown that GATA3 can inhibit metastasis and change the tumor microenvironment in BCa by inducing the expression of miR-29b [8]. miR-30c has also been shown to regulate *GATA3* transcription in breast tu-

mors [34]. However, the role of genetic variants in the 3′-untranslated region (3′UTR) of the *GATA3* gene and its post-transcriptional regulation have not been fully elucidated. Using the bioinformatics analysis, the researchers showed that rs1058240, located in the *GATA3* 3′UTR, contains binding sites of miRNA, involved in the post-transcriptional regulation of *GATA3* [45].

The previous results have shown a vital role of *GATA3* 3′UTR variants in the post-transcriptional regulation of mRNA expression. However, the association of *GATA3* transcriptional regulation with 3′UTR variations requires further verification to facilitate the development of new therapeutic strategies [8].

Also, there is preliminary evidence that *GATA3* enhances and stabilizes *ERS1* mRNA transcription, while progesterone-induced activation of the progesterone receptor causes the decrease of the *GATA3* expression. This may explain the connection between the presence of the mutations and the receptor status of BCa [44].

Another distinctive mutated region is AT-rich interaction domain 1A (ARID1A), which plays a role in inhibiting tumor growth and may contribute to the initiation and progression of BCa in young women [46, 47]. *ARID1A* deletion is an independent prognostic factor of invasive BCa. The low expression of *ARID1A* mRNA is determined in the samples of the luminal BCa subtypes and is associated with low overall survival. In addition, *ARID1A* may have a high value in predicting responsiveness to therapy. *ARID1A* mutation is most often detected in metastatic fulvestrant-resistant BCa. In addition, the deregulation of *ARID1A* is associated with resistance to paclitaxel and the targeted drugs in BCa patients [48].

The recent attempts to analyze a wider profile of gene expression related to the development of the specific biological processes and the formation of adaptive functional signatures allowed revealing a high level of expression of the components of the stromal microenvironment and its association with the composition of the immune infiltrate, metabolic activity, and vascularization processes. Tumor progression provokes an increase in collagen synthesis with the simultaneous growth of mesenchymal stem cells with signs of an immunosuppressive phenotype [49]. To date, it has been established that a characteristic feature of BCa in young patients is a low percentage of stroma and high indicators of the tumor-stromal ratio, compared to older women [50].

It is recognized that the stromal microenvironment of a tumor lesion is a complex and dynamic structure whose chemical and biophysical properties influence cell adhesion, proliferation, and migration. The main fibrillar component of the stroma is collagen, which makes up to 30% of the total protein mass in the human body. To date, 28 different types of collagens have been identified, which create a unique composition of the extracellular matrix in various tissues. It was established that the expression and deposition of collagen in the mammary gland of conditionally healthy premenopausal women varies depending on the stage of the menstrual cycle. The largest number of collagen fibers in the mammary gland is observed after the cessation of breastfeeding. At the same time, by their topology, such collagen fibers are most similar to the elements of the extracellular matrix of BCa [51].

It is known that the changes in the morphology, representation, and organization of collagen fibers in the process of malignant growth contribute to the formation of a unique microenvironment that stimulates tumor progression, primarily due to the influence on cell migration and polarization. In addition, the remodeling of collagen fibers in premetastatic areas is important for the survival and growth of the disseminated tumor cells. According to the data of the experimental studies [52], the cultivation of human BCa cells in the presence of the extracellular matrix using a 3D matrix led to an increase in their invasive activity in the case of young ECM

components compared to the aged components. Despite the proven role of the stromal microenvironment in the development and progression of BCa [53, 54], the molecular biological parameters of the disorganization and collagen expression indicators associated with the age of patients have not been definitively elucidated and require further research.

The functional state of the collagen framework depends on the activity of tumor-associated matrix metalloproteinases (MMPs). Depending on the functional specificity, all MMPs are divided into two main groups: collagenases (MMP-2, MMP-9) and gelatinases (MMP-1, MMP-8, MMP-13), as well as several minor groups. The main function of MMPs is the degradation of proteins and glycoproteins in the extracellular matrix. During malignant growth, MMPs communicate between the tumor and the stroma, which promotes infiltrating growth due to the activation of the cytokines and growth factors and the modification of the adhesion molecules. A high level of expression of MMP-14 in the stromal component of the tumor microenvironment was shown to correlate with the age of BCa patients [55]. Our research has confirmed the association of MMP-2 and MMP-9 with clinical and pathological features of BCa in young patients. It has been established that low MMP-2 mRNA levels against the background of increased expression of this gelatinase at the protein level, as well as decreased expression of *MMP9*, both at the mRNA and protein levels, are characteristic features of BCa in young patients. We identified the relationship between the expression of these gelatinases and such indicators of the BCa malignancy as tumor stage, the presence of regional lymph node metastases, and the molecular BCa subtypes in young patients [56].

The heterogeneity of the factors of the tumor microenvironment due to the expression of certain sets of the genes involved in the formation of the microenvironment landscape allows recognizing at least four variants of the disease course even within the framework of the triple negative molecular subtype of BCa [57].

Today, the prognostic value of the molecular BCa subtypes in young patients remains an open question. It was found that the survival rate of patients with luminal A and luminal B molecular BCa subtypes is significantly lower in young patients compared to older patients, while overall survival rates in different age groups of patients with basal and Her2/neu-positive BCa practically did not differ [58, 59]. Liu et al. [60] found that the luminal A molecular subtype is associated with low overall survival rates and a high risk of tumor recurrence in young women compared to patients older than 40 years.

According to the data of other recent clinical observations [61, 62], the most common molecular BCa subtype in young patients is luminal B which is diagnosed 10% more often in them compared with patients after 45 years old and is associated with a high level of regional lymph node metastasis [63]. At the same time, it has been found that the proliferative activity of BCa is an independent predictive factor of the disease course only in young women with the luminal B subtype [64].

Analysis of the transcriptome has helped to identify the pathways of the differential gene expression in various age groups of BCa patients differed by the regulation of the immune response and the peculiar metabolic patterns [65].

Today, it is recognized that aging is one of the key risk factors for cancer incidence, and cellular senescence and changes in the microenvironment are the basis of preparations for the end of the physiological cycle of the existence of a biological system. During tumor growth, senescent cells stimulate the production of a specific pool of molecules (senescence-associated secretory phenotype, SASP) (IL-6, IL-8, MMP-1, IL-1α, CXCL11, and GM-CS) that activates the proliferation of the transformed cells and promotes cancer progression [66]. Therefore, the role of the stromal components of the microenviron-

ment in the BCa features in patients of different age groups has been studied. The experimental data showed that increased mammographic density of the breast is a critical risk factor for the development of BCa that creates significant obstacles and limits the timely radiological and magnetic resonance detection of cancer in the early stages [20, 21, 67]. The lowest mammographic density and the content of the stromal component are identified in the hormone-resistant BCa cases, and a high level of fibrosis in the mammary gland is noted in young patients with regional lymph node metastases [68]. The above could be realized because of the different activities of the tumor-infiltrating lymphocytes and the varying host immune response.

Zhao et al. [69] found that a characteristic feature of BCa in elderly women is a high degree of infiltration by M2-macrophages against the background of a decrease in T-lymphocyte counts, compared to a group of young women [70]. At the same time, the greatest infiltration by macrophages was determined in the tissue of hormone-refractory BCa. According to Erbe et al. [71], the malfunction of macrophages and T-lymphocytes in the BCa tissue of older patients is caused by impaired IFNγ signaling.

In recent years, the prognostic value of the programmed death-ligand 1 (PD-L1) has been studied in BCa patients: PD-L1 is expressed on transformed cells, and its interaction with the PD1 receptor on the surface of immunocytes causes a suppression of antitumor immunity [72]. The independent studies by Qin et al. [73] and Xiang et al. [74] established that the BCa tissue of women under the age of 40 is characterized by significantly higher PD-L1 expression, compared to that of older patients. The association of the PD-L1 levels in the tumor tissue of young patients with the tumor stage, the presence of regional lymph node metastases, tumor differentiation grade, and receptor status was revealed.

Recently, the pan-immune-inflammation value (PIV) index, which reflects the ratio of the main cellular components of peripheral blood (monocytes, platelets, lymphocytes, and leukocytes), has been actively used in clinical practice to predict the aggressiveness of the course of cancer, including BCa, as well as a biomarker associated with the presence of an inflammatory process in the body. It was found that the PIV indices in the blood of young BCa patients were significantly higher compared to older women. These data indicate that acute inflammation can be the leading driver and risk factor for the development of aggressive forms of BCa in young patients [75, 76].

More attention is paid to the study of the role of microbiota in the development of systemic and local inflammation in cancer [77]. It is recognized that microorganisms are able to influence a number of physiological and pathological processes in the human body through the effects on the metabolic pathways, the alteration of the genetic material of cells, and the modulation of their signaling pathways. It is known that the mammary gland has its own specific microbiota, which is characterized by heterogeneity depending on the stage of the menstrual cycle and is heterogeneous even between two glands within the same organism [78]. It has been shown that in the mammary gland tissue of healthy donors, bacteria of the genera *Lactococcus, Streptococcus, Prevotella, Corynebacterium*, and *Micrococcus* predominate, while in the BCa tissue, there is observed a higher content of *Staphylococcus, Bacillus, Enterobacteriaceae, Comamonadaceae*, and *Bacteroidetes* [79].

The composition and functional activity of fecal microbiota are associated with the age and menstrual status of patients with BCa and also correlates with the estrogen concentration in the blood. It has been shown that in postmenopausal women with BCa, high levels of *Clostridiaceae, Faecalibacterium*, and *Ruminococcaceae* bacteria are determined against the background of low content of *Dorea* and *Lachnospiraceae* families compared to young patients with preserved

menstrual function [80]. A characteristic feature of the microbiota of young premenopausal women with BCa is also the presence of *Bacteroides fragilis* in the intestines, in contrast to older postmenopausal women, who have a greater number of intestinal *Klebsiella pneumoniae* [81]. These facts point to the prospects of further research aimed at determining the diagnostic and prognostic values of the composition of the microbiota in young patients with BCa for the development of individualized prevention programs.

To sum up, the analysis of the literature data along with the systematization of our own data recognizes that in spite of the immense progress in understanding the etiology and pathogenesis of BCa, this disease remains among the major current medial-and-biological problems especially with taking in account a tendency toward an increase in the BCa incidence in young women. The young age is believed an independent unfavorable prognostic factor of BCa, which is associated with an unfavorable prognosis and low survival rates and is considered an important predictor of the disease aggressiveness with a high risk of metastasis and recurrence. In patients of young age, the incidence of advanced BCa with metastases to the lymph nodes and remote metastases is higher than in patients aged over 45. Furthermore, in young patients, luminal B and basal subtypes with high proliferative activity are diagnosed more frequently. According to the current concept, the pathogenesis and aggressiveness of BCa depend not only on the clinical-pathological and molecular-genetic characteristics but also on the metabolic disorders and aging facilitating the formation of an aggressive microenvironment of the tumor lesion. The association between the high expression of the components of the stromal microenvironment and the inflammatory immune infiltrate as well as the increased vascularization of the tumor lesion has been found in the BCa tissue of young patients. The acute inflammation is considered one of the key drivers and risk factors of this disease. At the same time, the association of age and menstrual status with the composition and functional activity of microbiota affecting the formation of the molecular profile of neoplasms has been finally confirmed. Proving the nature of the formation of the landscape comprising molecular-genetic, cytokine, and immune factors of the tumor microenvironment will undoubtedly contribute to our understanding of the mechanisms of tumor growth allowing for the development of algorithms for delineating the groups at high risk of tumor progression that require more careful monitoring and personalized treatment approach. This will be helpful in the development of innovative technologies for complex BCa treatment in both young and aged patients.

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РАК ГРУДНОЇ ЗАЛОЗИ У ЖІНОК МОЛОДОГО ВІКУ:
ПОШУК ШЛЯХІВ ОПТИМІЗАЦІЇ ДІАГНОСТИКИ
ТА ПЕРСОНІФІКОВАНОГО ЛІКУВАННЯ

Статистичні дані останніх десятиріч свідчать про неухильне зростання показників захворюваності на рак грудної залози (РГЗ) серед жінок молодого віку, який посідає перше місце у структурі захворюваності пацієнток віком 18—29 років та є однією із провідних причин смертності у віковому діапазоні 15—39 років. За даними епідеміологічних досліджень та клінічних спостережень, молодий вік є незалежним прогностичним фактором РГЗ, який асоціюється з агресивним перебігом пухлинного процесу, високим ризиком виникнення метастатичних уражень та рецидивів, а також низькими показниками виживаності хворих. Варіабельність РГЗ у хворих різних вікових груп за клініко-патологічними та молекулярно-біологічними ознаками, а також перебігом захворювання і відповіддю на проведену терапію опосередкована багатьма чинниками. У сучасній літературі активно опрацьовується концепція, згідно з якою провідна роль у патогенезі РГЗ належить не лише молекулярно-генетичним змінам, а й метаболічним порушенням, спричиненим особливостями сучасного соціально-побутового ритму життя, структури харчування та старінням, які впливають як на загальний стан організму, так і на формування агресивного мікрооточення пухлинного вогнища. Особливості ідентифікованого транскриптому та шляхи диференційної експресії генів свідчать про відмінності факторів регуляції імунної відповіді та метаболічних процесів у різних вікових групах хворих на РГЗ. Виявлено асоціацію високого рівня експресії компонентів стромального мікрооточення у тканині РГЗ хворих молодого віку з наявністю запального імунного інфільтрату та посиленими процесами васкуляризації пухлинного вогнища. Розгадка природи формування ландшафту молекулярно-генетичних, цитокіново-ростових та імунних факторів пухлинного мікрооточення допоможе зрозуміти механізми пухлинного росту та створити алгоритм формування груп високого ризику прогресування пухлинного процесу, які потребують більш ретельного моніторингу та персоналізованого підходу до лікування, що сприятиме розробці інноваційної технології комплексного лікування хворих на РГЗ як молодого, так і похилого віку.

Ключові слова: рак грудної залози у молодих жінок, клініко-патологічні та молекулярно-біологічні ознаки, пухлинне мікрооточення.