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PATTERN OF MMP2 AND MMP9 EXPRESSION DEPENDS ON BREAST CANCER PATIENTS' AGE

Background. Despite the large number of studies devoted to the exploration of the features of tumor microenvironment in breast cancer (BCa), presently there is no consensus on the features of MMP-2 and MMP-9 expression in the tumor tissue of BCa patients depending on the age. **The aim** of the study was to investigate the relationship between MMP-2 and -9 expression at the protein and mRNA levels in BCa tissues and the clinical and pathological features of BCa patients in different age groups. **Materials and Methods.** The expression level of MMP-2 and -9 in the BCa tissue of patients of two age groups (<45 years and >45 years) was studied using the bioinformatics method (UALCAN database), immunohistochemical method, and real-time PCR. **Results.** It was established that a characteristic feature of BCa in young patients is the low level of *MMP2* mRNA against the background of increased expression of this gelatinase at the protein level, as well as decreased expression of *MMP9* at both the mRNA and protein levels. When analyzing the correlation of the gelatinase expression indices in BCa tissue of young patients, depending on the clinical and pathological features, a significantly lower level of MMP-2 expression was recorded in BCa cases of stage II compared to the indices of stage I cases. High expression of MMP-2 and -9 was recorded in BCa tissue in node-positive cases and the basal molecular BCa subtype. **Conclusions.** The identified relationship between the expression of the studied gelatinases and such indices of BCa malignancy as its stage, positive regional lymph node status, and the molecular BCa subtype in young patients indicates the need for further research of the features of the tumor microenvironment to predict the cancer aggressiveness.

Keywords: breast cancer, matrix metalloproteinases, MMP-2, MMP-9.

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The statistical data of the last decades indicate a steady increase in the incidence of breast cancer (BCa), especially among young patients. It is known that cancer in young patients differs from that in older people in the aggressiveness of the clinical course, histological structure, and molecular profile. It is known that young women have a higher risk of recurrence, the development of secondary BCa, as well as lower survival rates [1]. Young BCa patients also have a high frequency of the triple-negative (basal) molecular BCa subtype, which is characterized by an aggressive course and low sensitivity to chemotherapy [2]. Therefore, the search for the factors that would allow predicting the aggressive potential of BCa in this prognostically unfavorable group of patients remains one of the most urgent tasks of modern oncology.

In recent years, it has been conclusively proven that the tumor microenvironment plays a key role in the progression of many malignant neoplasms, including BCa [3—5]. It is a complex dynamic system consisting of an extracellular matrix, stromal and immune cells, a network of blood and lymphatic vessels, as well as a large number of proteins [6].

One of the most widespread non-cellular elements of the microenvironment is the family of 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 MMP is the degradation of proteins and glycoproteins of the extracellular matrix (ECM). MMPs are involved in many vital biological processes, such as tissue repair and remodeling, differentiation, proliferation, migration, apoptosis, and angiogenesis. In malignant growth, MMPs communicate between the tumor and the stroma, which promotes the infiltrating growth via the activation of cytokines and growth factors, as well as the modification of adhesion molecules [7, 8]. MMP-2 and -9 are the most studied among the known MMPs. They are activated in the intercellular matrix under the action of chymase, as well as superoxide radicals formed in the mitochondria of tumor cells and/or produced by neutrophils. Such activation enhances the invasion and metastatic potential of the neoplasm [9, 10].

According to recent data, the level of MMP-2 and MMP-9 expression in BCa tissue is 10 times higher than that in benign neoplasms. In addition, their expression indices correlate with the presence of metastases in regional lymph nodes. Therefore, these proteins can be considered as potential biomarkers for the detection of BCa. Despite the large number of studies devoted to the study of tumor microenvironment in BCa, presently there is no unified point of view on the features of expression of MMP-2 and 9 in tumor tissue of BCa patients of different age groups [11, 12].

Therefore, the aim of the work was to study the relationship between the *MMP2* and *MMP9* expression indices at the protein and mRNA levels in BCa tissue and the clinicopathological features of BCa patients in different age groups.

Materials and Methods

Patients. The study was conducted on the postoperative material of 60 patients with stage I, II BCa who were treated at the National Cancer Institute of the Ministry of Health of Ukraine, Kyiv Clinical Oncology Center, and Kyiv Regional Oncology Dispensary within 2015—2022 and gave informed consent for the use of clinical data for scientific purposes. All patients before surgery received neither radiation treatment nor chemotherapy and were examined using conventional clinical and laboratory methods according to the standards of diagnosis and treatment of cancer patients approved by Order No. 554 of 17.09.2007 of the Ministry of Health of Ukraine. Tissue samples were encoded and depersonalized. The general clinical characteristics of the patients are presented in Table 1.

Immunohistochemical method. The expression of MMP-2 and MMP-9 was studied on paraffin sections (4—6 μm) of postoperative BCa material. MMP-2 MoAbs (clone 2C1-1D12) (Thermo Scientific, USA) (dilution 1:50), and MMP-9 (clone MA5-15886) (Thermo Scientific, USA) (dilution 1:150) were used as primary antibodies. The UltraVision LP Detection System kit (Thermo Scientific, USA) was used to visualize the reaction according to the manufacturer's recommendations. Sections were stained with Mayer's hematoxylin. The expression of molecular markers was evaluated by the H-Score method [13].

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). Total RNA from BCa tissue was isolated using the commercial kit "TRI" (QIAGEN, Germany) according to the manufacturer's recommendations. The amount of isolated RNA was determined using a spectrophotometer "NanoDrop 2000c Spectrophotometer" (Thermo Scientific, USA). To study mRNA expression of *MMP2* and *MMP9* genes, single-stranded DNA was synthesized from 100 ng of total RNA using the LunaScript RT SuperMix Kit (New England Biolabs Inc., USA) for reverse transcription. For qRT-PCR, verified primers [14] synthesized by Metabion, Germany, were used. The relative expression of *MMP2* and *MMP9* mRNA was determined by the comparative CT method [15]. The qRT-PCR analysis was performed on a QuantStudio 5 Dx Real-Time PCR System (Thermo Scientific, USA).

Bioinformatics method. Comparison of the studied gene expression levels (mRNA and protein) in BCa tissue in relation to similar data on non-malignant breast cells, as well as the relationship of their expression with the main clinicopathological characteristics of the tumor process, was carried out using the University of Alabama at Birmingham CANcer data analysis Portal — UALCAN (http://ualcan.path.uab.edu/index.html). The values of mRNA expression of the studied genes are presented as Transcripts Per Million (TPM). It is a normalization method for RNA-seq, which should be read as "N copies of particular genes mRNA for every 1,000,000 RNA molecules in the RNA-seq sample. Expression of genes at the protein level was presented as Z-values — the standard deviations from the median expression across samples.

Statistical methods. Statistical analysis of the results was performed using the GraphPad Prism v.8.0 program (GraphPad Software Inc., USA) taking into account the nature of the distribution of the obtained data. Testing of the statistical hypothesis about the normality of the distribution was carried out using Student's *t*-test (for a parametric distribution) or the Mann — Whitney U-test (for a non-parametric distribution). $p < 0.05$ was considered to indicate statistically significant differences. Data are presented as M ± m (where M is the mean, m is the standard error of the mean) or as a percentage for relative values.

Table 1. **Clinicopathological characteristics of the patients with BCa**

Characteristics	≤45 years group		>45 years group	
	N	%	N	%
Number of patients	28	46.6	32	53.3
Patients age (years)				
Average age	39.05 ± 5.9		64.3 ± 10.5	
Age range	28—45		46—89	
BCa stage				
I	10	35.7	10	31.2
II	18	64.3	22	68.8
Category N according to TNM				
N0	18	64.3	20	62.5
N1	10	35.7	12	37.5
Molecular subtype				
Luminal	20	71.4	19	19
Basal	8	28.6	13	13

Results and Discussion

Bioinformatics analysis. The bioinformatics analysis carried out with the help of the UALCAN online resource established that the level of mRNA expression of the *MMP2* gene in non-transformed breast tissue was 251.0 TPM within the range from 28.0 to 657.8 TPM and practically did not differ from similar indices in BCa tissue (207.0 TPM within the range from 5.6 to 767.7 TPM). In contrast, the development of malignant neoplasms in the mammary gland was accompanied by an 8-fold ($p < 0.05$) increase in the mRNA level of the *MMP9* gene in BCa cells compared to normal breast tissue (Fig. 1, *a*—*b*).

Analysis of the expression indices of the studied genes at the protein level demonstrated that BCa tissue was also characterized by a 16-fold decrease ($p < 0.05$) at the expression level of MMP-9 (Fig. 1, *d*) compared to non-transformed breast tissue. No significant differences in MMP-2 expression indices were found (Fig. 1, *c*).

According to the data of bioinformatics analysis, the expression of both studied MMPs was associated with the age characteristics of BCa patients only at the mRNA level (Fig. 2). The highest levels of *MMP2* and *MMP9* were recorded in the BCa tissue of patients aged 41 to 60 years (230.39 and 39.036 TPM, respectively) ($p < 0.05$) compared to the group of patients aged 21—40 years.

When analyzing the expression indices of the studied genes depending on the main clinicopathological characteristics of BCa, we have found that a characteristic feature of stage II BCa is low values of *MMP2* mRNA expression ($p < 0.05$), compared to BCa of stages I and III. A significantly lower level of *MMP2* mRNA expression was also noted in the tissue of triple-negative BCa compared to neoplasms of luminal and HER2/neu-positive molecular subtypes. No correlation between the expression of *MMP2* at the mRNA level and the status of metastatic lesions of the lymph nodes was found.

The highest level of MMP-2 expression at the protein level ($p < 0.05$) was recorded in BCa tissue of patients with stage I compared to BCa of stages II and III. No statistically significant difference in the expression of this gene at the protein level was found in the BCa tissue of different molecular subtypes (Fig. 3).

A significant decrease in the level of *MMP9* mRNA ($p < 0.05$) was recorded in neoplasms of patients with N3 status compared to similar indices of BCa cases of categories N0 and N1. No difference in *MMP9* mRNA expression was detected depending on the stage and molecular subtype of BCa.

A high level of MMP-9 ($p < 0.05$) was determined in neoplasms of HER2/neu-positive and triple-negative molecular BCa subtypes in comparison with tumors of both luminal subtypes. No statistically significant difference in MMP-9 expression indices was found depending on the stage of the disease (Fig. 4).

So, the analysis of the open database permits us to establish that the mRNA level of both investigated gelatinases is associated with the age characteristics of patients and the stage of BCa, while the expression of MMP-2 and MMP-9 depends on the molecular subtype of BCa and the presence of metastatic lesions of regional lymph nodes. The relationship between the expression of MMP-9 at the protein level and the molecular BCa subtype was noted. The obtained data confirm the expediency of studying MMP-2 and MMP-9 expression indices in the BCa tissue of patients of different age groups.

Study of the expression of MMP2 and MMP9 in BCa patients of different age groups. At the following stage of the study, the expression indices of *MMP2* and *MMP9* at the protein and mRNA levels in the BCa tissue of patients of different age groups were analyzed (the characteristics of the studied groups are presented in Table 1). As can be seen from the data presented in Table 2, the level of *MMP2* mRNA was twice higher in the BCa tissue of patients under the age

of 45 ($p < 0.05$), while the level of MMP-2 expression at the protein level was increased by 45% in the BCa tissue of patients older than 45 years.

We have shown that a characteristic feature of BCa in young patients was a decrease in the expression of *MMP9* both at the mRNA level and at the protein level (by 3.9 and 2.9 times, respectively, $p < 0.05$) in comparison with similar indices of BCa patients older than 45 years.

When studying the features of expression of gelatinases depending on the stage of the tumor process, a higher level of *MMP2* mRNA (by 2.5 times, $p < 0.05$) was recorded in the tumor tissue of younger women with stage I BCa compared to patients of the same age with stage II BCa (Fig. 5). In the tumor tissue of patients older than 45 years with stage II BCa, there was observed a decrease in the expression of MMP-9 at the protein level (by 35%, $p < 0.05$) compared to that in stage I cases.

A characteristic feature of BCa in young patients with metastatic lesions in regional lymph nodes was a low expression of *MMP2* at the mRNA level (0.4581 a.u. ($p < 0.05$)) and a high level of MMP-2 expression at the protein level (164.7 H-score points ($p < 0.05$)).

In the tumor tissue of young BCa patients with metastatic lesions of the regional lymph nodes, an increase in *MMP9* expression at both the mRNA and protein levels was determined (by 5.6 and 2.7 times, respectively, $p < 0.05$).

In patients older than 45 years with metastatic lesions in the regional lymph nodes, an increase in the expression of *MMP9* was noted only at the mRNA level (by 2.7 times ($p < 0.05$)) compared to that in patients without metastases (Fig. 6).

Certain differences were found when analyzing the dependence of gelatinase expression on the molecular subtype of BCa. It was demonstrated that *MMP9* expression at the mRNA level was 8.6 times higher ($p < 0.05$) in the basal BCa subtype tissue of patients younger than 45 years compared to the patients with luminal BCa subtype. It was established that the basal BCa subtype samples in patients under the age of 45 were characterized by higher levels of expression of MMP-2 ($p < 0.05$) and MMP-9 ($p < 0.05$) proteins compared to the luminal BCa subtype

Table 2. **Expression of gelatinase genes at the mRNA and protein levels in BCa tissue of patients of different age groups**

Gene		*MMP2*		*MMP9*	
Age	Parameter	mRNA (a.u.)	Protein (H-score points)	mRNA (a.u.)	Protein (H-score points)
≤45 years	Min	0.1322	0	0.02127	0
	Q1	0.5073	40	0.08161	16.25
	Median	**0.8183***	**120***	**0.8228***	**57.5***
	Q3	1.326	158	0.398	147.5
	Max	7.018	175	4.469	175
>45 years	Min	0.001969	65	0.02499	130
	Q1	0.02614	130	0.9993	160
	Median	**0.1741**	**150**	**2.088**	**210**
	Q3	0.7004	162	4.767	246.5
	Max	5.614	250	18.75	265

Note: * the difference is significant in comparison with the older patients ($p < 0.05$).

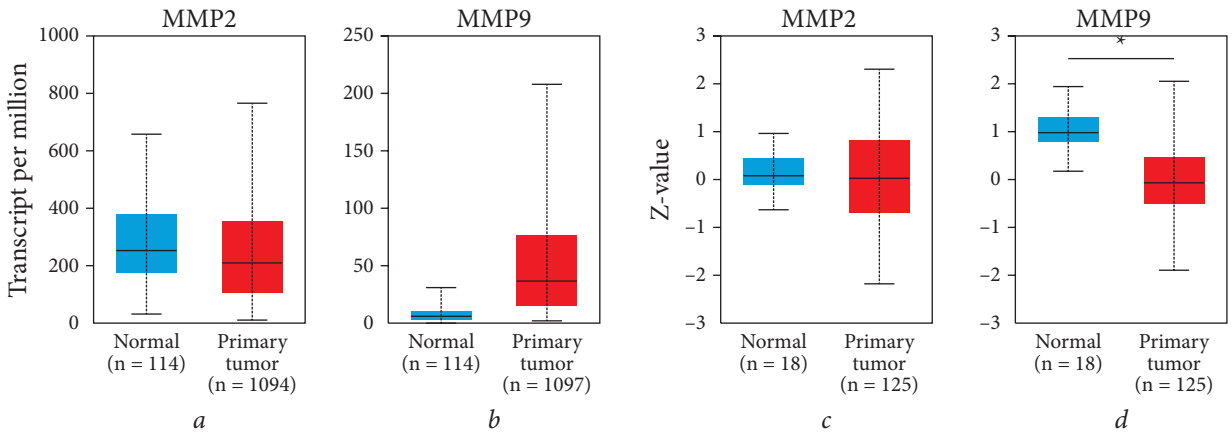

Fig. 1. Expression of *MMP2* and *MMP9* at the mRNA (*a, b*) and protein (*c, d*) levels in normal and malignantly transformed breast tissue according to UALCAN (*$p < 0.05$)

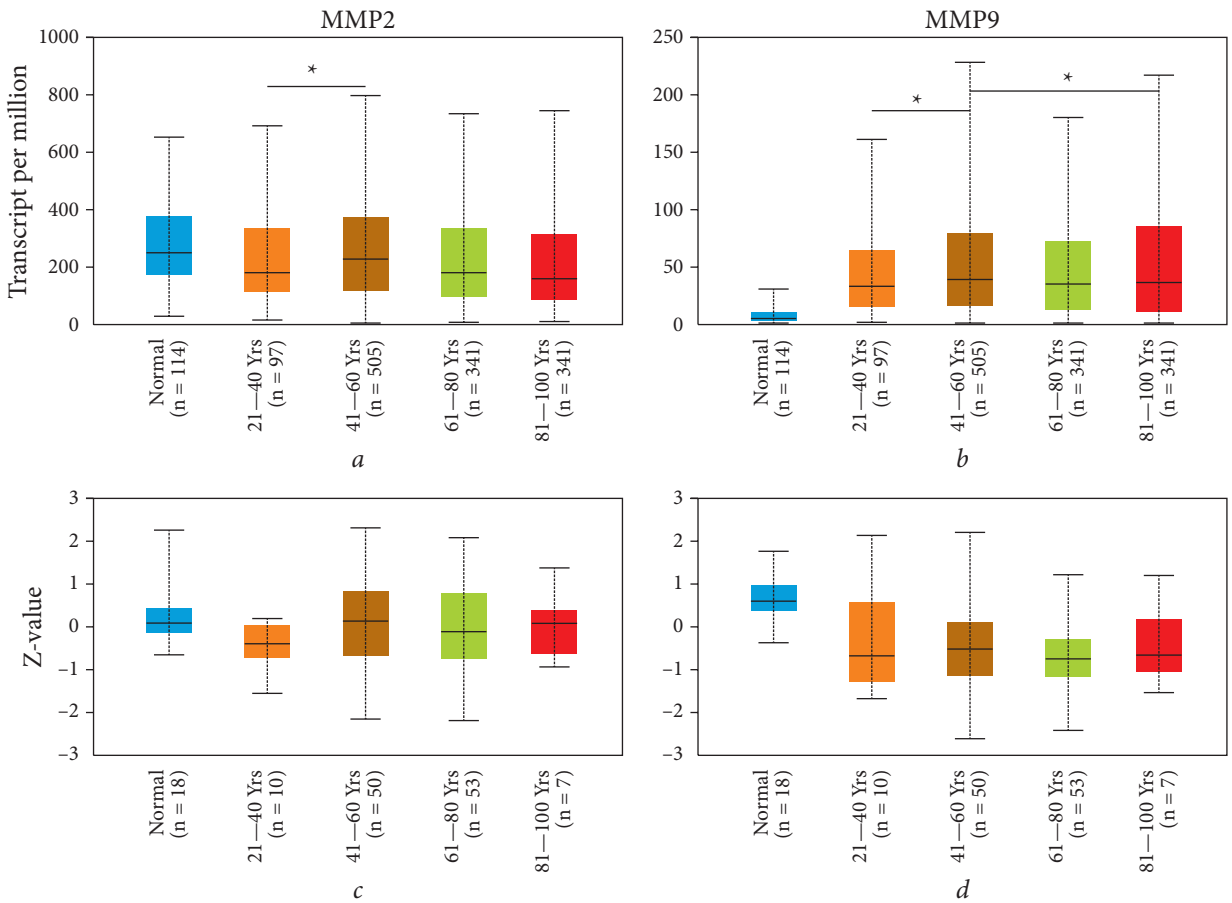

Fig. 2. Relationship of *MMP2* and *MMP9* expression indices at the mRNA (*a, b*) and protein (*c, d*) levels with the age of BCa patients (*$p < 0.05$) according to UALCAN

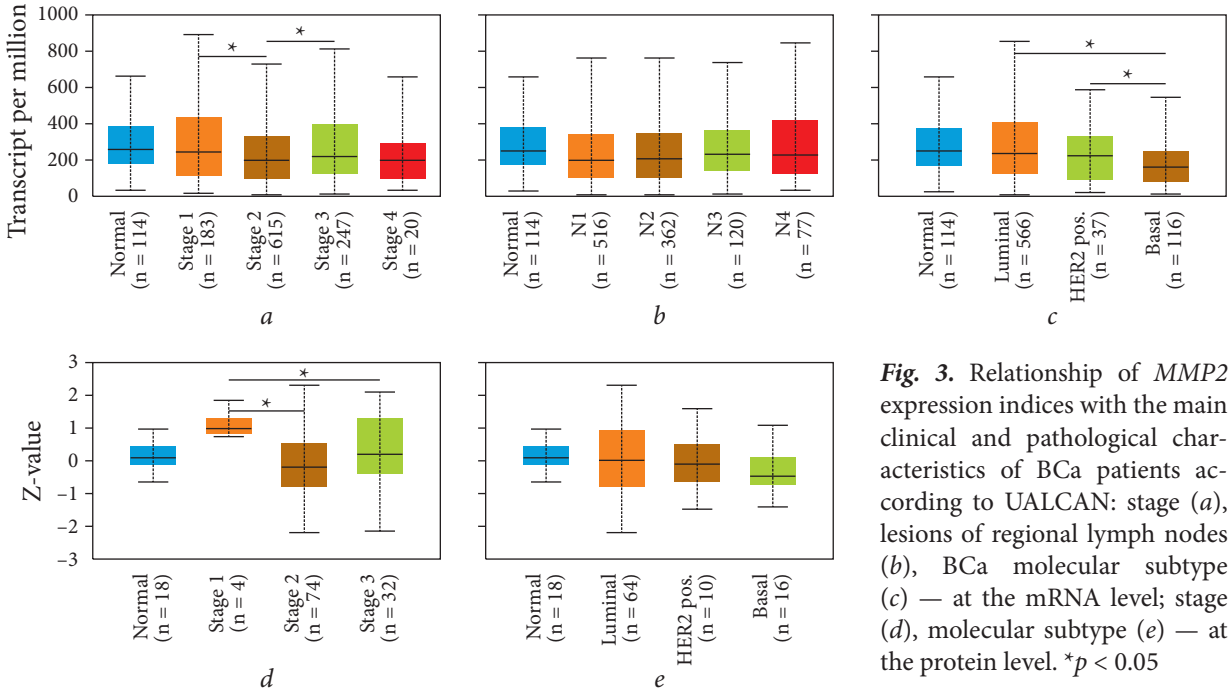

Fig. 3. Relationship of *MMP2* expression indices with the main clinical and pathological characteristics of BCa patients according to UALCAN: stage (*a*), lesions of regional lymph nodes (*b*), BCa molecular subtype (*c*) — at the mRNA level; stage (*d*), molecular subtype (*e*) — at the protein level. *$p < 0.05$

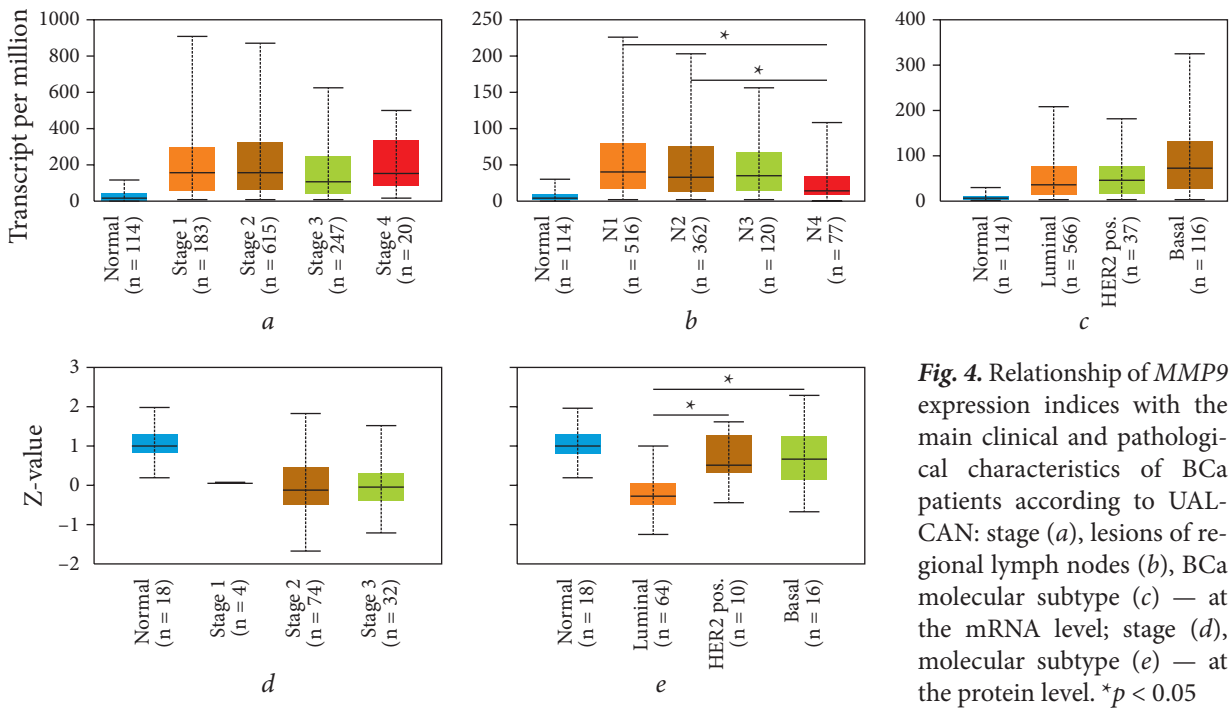

Fig. 4. Relationship of *MMP9* expression indices with the main clinical and pathological characteristics of BCa patients according to UALCAN: stage (*a*), lesions of regional lymph nodes (*b*), BCa molecular subtype (*c*) — at the mRNA level; stage (*d*), molecular subtype (*e*) — at the protein level. *$p < 0.05$

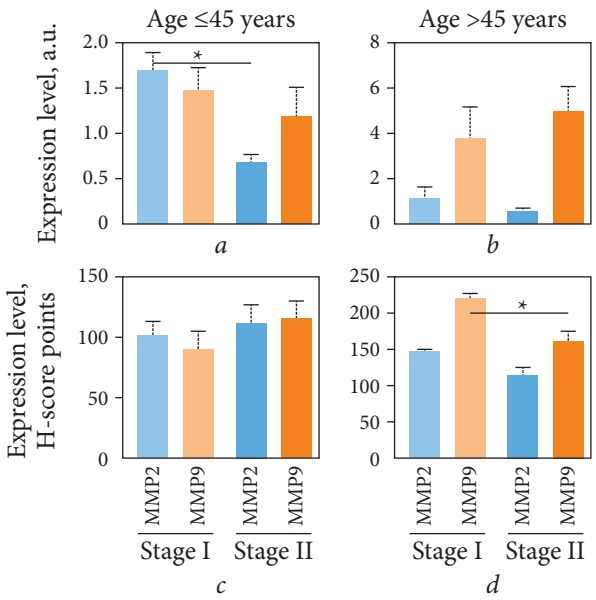

Fig. 5. Indices of *MMP2* and *MMP9* expression at the levels of mRNA (*a, b*) and the protein (*c, d*) in the BCa tissue of patients of different age groups depending on the stage of the disease. **p* < 0.05

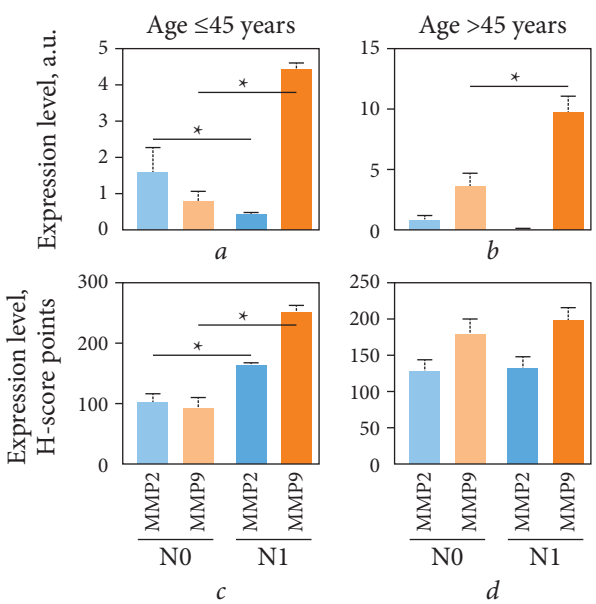

Fig. 6. Indices of *MMP2* and *MMP9* expression at the levels of mRNA (*a, b*) and the protein (*c, d*) in the BCa tissue of patients of different age groups depending on the status of regional lymph nodes. **p* < 0.05

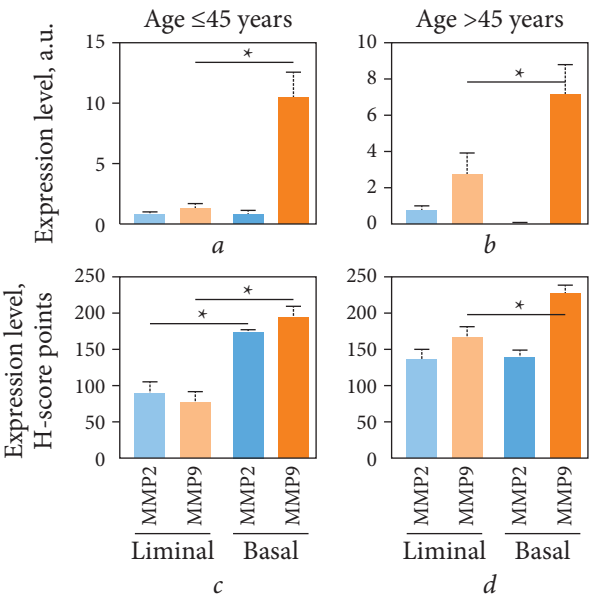

Fig. 7. Indices of *MMP2* and *MMP9* expression at the levels of mRNA (*a, b*) and the protein (*c, d*) in the BCa tissue of patients of different age groups depending on the molecular BCa subtype. **p* < 0.05

samples in patients of the same age group. It was shown that the expression of *MMP9* mRNA and MMP-9 protein in the BCa tissue of patients older than 45 years increased by 2.8 ($p < 0.05$) and 1.4 ($p < 0.05$), respectively (Fig. 7).

So, our study allowed us to identify the expression profile of gelatinases at the mRNA and protein levels in BCa patients of different age groups. It has been established that a characteristic feature of BCa in young patients is low levels of *MMP2* mRNA 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, compared to the neoplasms of patients older than 45 years.

The different directions in changes of *MMP2* gene expression at the mRNA and protein levels comparing patients older and younger than 45 years can be probably explained by the features of its post-transcriptional regulation. In particular, according to literature data, post-transcriptional regulation of *MMP2* expression is influenced by

mRNA stability, the efficiency of protein translation itself, and miRNA-based mechanisms. Hypoxia, hyperglycemia, pH, reactive oxygen species, and lipid peroxidation affect the post-transcriptional regulation of MMP expression.

When analyzing the correlation of gelatinase expression indices in BCa tissue of young patients depending on the clinical and pathological features, a significantly lower level of MMP-2 mRNA expression was identified in stage II BCa patients compared to stage I. Significantly higher expression levels of two studied gelatinases both at the mRNA and protein levels were recorded in BCa tissue in the cases with metastasis in regional lymph nodes. In BCa patients older than 45 years, an inverse relationship between the expression of MMP-9 at the protein level and the stage of the tumor process was established along with a direct relationship between the mRNA level of this gelatinase and the presence of regional lymph node metastasis. The decreased levels of MMP-9 mRNA and protein were recorded in the luminal BCa subtype cases in the older age group.

In the available literature, there are only some reports regarding the relationship between the expression of gelatinases and the age and clinicopathological features of patients with BCa. Têtu et al. [16] found no relationship between the MMP-2 protein levels and the age of BCa patients. Kuskunović-Vlahovljak et al. [17] showed that in the group of patients younger than 50 years, tumors with low expression of MMP-2 and high levels of MMP-9 are more common, but no correlation was observed between the levels of these gelatinases in BCa tissue and the age of patients, regional lymph node metastasis, hormonal status, and other clinicopathological characteristics. Other researchers found that a high level of MMP-2 expression in BCa tissue correlated with low rates of recurrence-free survival in young patients with node-positive breast neoplasms compared to patients over 40 years [18]. Song et al. [19] demonstrated the relationship between the level of MMP-2 in the serum of young BCa patients at the time of diagnosis and the hormonal status and tumor differentiation grade.

Thus, up-to-date there is no single point of view regarding the features of MMP-2 and -9 expression in the BCa tissue of young patients. We have identified the relationship between the expression of MMP-2 and -9 and such indices of BCa as its stage, regional lymph node metastases, and the molecular subtype in young patients. These data indicate the need for further research on the features of the tumor microenvironment to predict the aggressiveness of the course of the disease.

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ХАРАКТЕР ЕКСПРЕСІЇ ГЕНІВ MMP2 ТА MMP9 У ТКАНИНІ РАКУ МОЛОЧНОЇ ЗАЛОЗИ ХВОРИХ РІЗНИХ ВІКОВИХ ГРУП

Вступ. Попри велику кількість досліджень, присвячених вивченню особливостей пухлинного мікроточення при раку молочної залози (РМЗ), на сьогодні не існує єдиної точки зору щодо особливостей експресії матриксних металопротеїназ (ММР-2 та 9) у пухлинній тканині хворих молодого віку. **Мета.** Дослідити зв'язок показників експресії генів *MMP2* та *MMP9* на рівні білка та мРНК у тканині РМЗ з клініко-патологічними особливостями пухлинного процесу хворих різних вікових груп. **Матеріали та методи.** Рівень експресії ММР-2 та -9 у тканині РМЗ хворих різних вікових груп досліджували з використанням біоінформативного

аналізу (база даних UALCAN), імуногістохімічного методу та ПЛР в реальному часі. Статистичну обробку результатів виконували за допомогою програми GraphPad Prism v.8.0 з урахуванням характеру розподілу отриманих даних. **Результати.** Встановлено, що характерною ознакою РМЗ хворих молодого віку є низькі показники мРНК *MMP2* на тлі підвищення експресії цієї желатинази на рівні білка, а також зниження експресії *MMP9* як на рівні мРНК, так і на рівні білка. При аналізі зв'язку показників експресії желатиназ у тканині РМЗ хворих молодого віку залежно від клініко-патологічних особливостей пухлинного процесу достовірно менший рівень експресії ММР-2 зафіксовано у тканині РМЗ стадії II порівняно із показниками хворих стадії I. Високу експресію ММР-2 та -9 зафіксовано у тканині РМЗ за наявності метастатичного ураження реґіонарних лімфатичних вузлів та при базальному молекулярному підтипі РМЗ. **Висновки.** Ідентифіковано зв'язок експресії досліджених желатиназ з такими показниками злоякісності РМЗ як стадія, наявність метастатичного ураження реґіонарних лімфатичних вузлів та молекулярний підтип новоутворень у пацієнток молодого віку свідчить про необхідність подальшого дослідження особливостей пухлинного мікрооточення для прогнозування агресивності перебігу пухлинного процесу.

Ключові слова: рак молочної залози, матриксні металопроотеїнази, ММР-2, ММР-9.