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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

INVESTIGATION OF NEW BIOMARKERS IN THE DIAGNOSIS OF BREAST CANCER

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Field of science: Biology

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GENERAL CHARACTERISTICS OF THE RESEARCH

The relevance of the problem. Breast cancer (BC) is the most common malignant tumor among women both worldwide and in our country, ranking second after lung cancer[1]. The incidence of BC, which is increasing globally every year, reached nearly 2 million women in 2021.[2] Although in recent years this problem, alongside other gynecological disorders, has been increasingly encountered in young women, it is observed predominantly in women aged 55–70 years. Late presentation of patients is reported in most cases as the main reason for the increase in BC mortality.[3]

According to the World Health Organization (WHO), approximately 2.4 million women were diagnosed with BC for the first time in 2024, and 694,000 deaths from this disease were registered in the same year.[4] The disease is particularly widespread in developed countries; however, in recent years an increasing trend in its prevalence has also been observed in developing countries. In countries with a very high Human Development Index, this type of cancer affects 1 in 12 women, while the ratio of women dying from it is 71:1.[5]

According to WHO data, in 2022 BC outnumbered all other types of cancer in 157 of 185 countries worldwide. BC ranks second

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[1] Bray, F. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries / F. Bray, J. Ferlay, I. Soerjomataram [et al.] // CA: A Cancer Journal for Clinicians, – 2018, vol. 68 (iss. 6), – p. 394-424.

[2] Filho, A.M. The GLOBOCAN 2022 cancer estimates: data sources, methods, and a snapshot of the cancer burden worldwide / A.M. Filho, M. Laversanne, J. Ferlay [et al.] // International Journal of Cancer, – 2025, vol. 156 (iss. 7), – p. 1336-1346.

[3] Farkas, A.H., Nattinger, A.B. Breast cancer screening and prevention // Annals of Internal Medicine, – 2023, vol. 176 (iss. 11), – p. ITC161-ITC176.

[4] World Health Organization. Breast cancer: prevention and control: [Electronic resource] // World Health Organization, – 2026. URL: https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[5] Manirakiza, A.V.C., Pfaendler, K.S. Breast, ovarian, uterine, vaginal, and vulvar cancer care in low- and middle-income countries: prevalence, screening, treatment, palliative care, and human resources training // Obstetrics and Gynecology Clinics, – 2022, vol. 49 (iss. 4), – p. 783-793.

in cancer mortality among women worldwide[6]. In 2021, BC accounted for up to 20% of all cancer cases registered in Azerbaijan. In the same year, cancer was the second leading cause of death in our Republic. Although female sex (99%) is one of the risk factors for the development of BC, men account for 0.5–1% of individuals diagnosed with this disease[7].

In Azerbaijan, BC is the most common type of cancer among women, and its incidence has been rising in recent years. Thus, according to the State Statistical Committee of the Republic of Azerbaijan, while 1,960 cases of BC were registered in 2020, this figure increased to 2,638 in 2021 and to 2,541 in 2023. When the statistics of malignant neoplasms in the population are considered by individual localizations, BC ranks first, lung cancer second, and gastric cancer third. Thus, in 2023 lung cancer was detected and registered in 1,461 persons and gastric cancer in 1,363 persons. In the same year, the total number of patients registered in medical institutions with a first-time diagnosis of a malignant tumor was 13,666, while the total number of registered patients diagnosed with malignant tumors in the Republic was 69,435. This means that in 2023 BC accounted for 18% of all malignant tumor cases in the Republic of Azerbaijan. This proportion was 16.9% of the total malignant tumor incidence in 2020, 19.3% in 2021, and 18.4% in 2022. The statistical report for 2024 shows that the number of women diagnosed with breast cancer in Azerbaijan has reached its highest level in the last 24 years. Thus, in 2024, BC was detected in 2,666 of 8,051 women first diagnosed with a malignant tumor; this figure was 2,523 in 2023 and 2,545 in 2022. Of the 157 thousand female patients with malignant neoplasms on the state register in 2024, 52 thousand were patients receiving treatment for BC.

The etiology of this disease, which in the absence of early

[6] Sung, H. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries / H. Sung, J. Ferlay, R.L. Siegel [et al.] // CA: A Cancer Journal for Clinicians, – 2021, vol. 71 (iss. 3), – p. 209-249.
[7] Scagliotti, M.F., Boietti, B.R., Knoblovits, P. Prevalence of men's health history in male breast cancer patients // Endocrinología, Diabetes y Nutrición, – 2020, vol. 70 (iss. 6), – p. 415-420.

diagnosis and adequate treatment leads to invasion of other organs and ultimately to death, is associated with various factors. Age, sex, obesity, harmful habits, radiation exposure, early onset of reproductive processes, late first pregnancy and hereditary factors increase the risk of BC. Age and sex are among the most important factors: female sex and age >40 years account for approximately 50% of BC cases.[8]

A family history of BC, especially the detection of this type of cancer in a male family member, carries a higher risk. Nevertheless, the absence of a family history of BC does not mean freedom from the risk of developing this disease in the future. The combined effect of various factors indicates that every woman is at risk.[9]

Although the development of radiological examinations and of immunological and immunohistochemical laboratory methods has created broad opportunities for solving the problems encountered in the diagnosis and prognostic assessment of BC, the dynamics of the increase in the disease indicate that the problem remains relevant.[10]

Although extensive investigation of immunohistochemical markers and partial elucidation of the mechanisms of tumor cell development have led to the wider use of targeted therapy methods and increased effectiveness of anticancer measures, the number of women suffering from the disease continues to grow.[11]

Object of the research. The study cohort was selected from among women who presented with breast pathologies to the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan (NOC MH RA) in 2023–2024. Breast tissue material was

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[8] El Masri, J., Phadke, S. Breast cancer epidemiology and contemporary breast cancer care: a review of the literature and clinical applications // Clinical Obstetrics and Gynecology, – 2022, vol. 65 (iss. 3), – p. 461-481.

[9] Easton, D.F. Gene-panel sequencing and the prediction of breast-cancer risk / D.F. Easton, P.D. Pharoah, A.C. Antoniou [et al.] // New England Journal of Medicine, – 2015, vol. 372 (iss. 23), – p. 2243-2257.

[10] Axundova, C.N., Sultanova, M.C., Qasımov, N.V. Süd vəzi xərçənginin diaqnostikasında radioloji görüntüləmə üsulları // Sağlamlıq, – 2021, №2, – s. 35-39.

[11] Allison, K.H. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update / K.H. Allison, M.E.H. Hammond, M. Dowsett [et al.] // Journal of Clinical Oncology, – 2020, vol. 38 (iss. 12), – p. 1346-1366.

classified in the pathohistology laboratory of the Center. Based on the laboratory results, groups were formed according to the expression of HER-2 and hormone receptors. The results of 89 women were included in the study. Of these, 15 were practically healthy women of reproductive age, 33 were women with HER-2-positive BC, 33 with HER-2-negative BC, and 8 with "triple-negative" BC. According to the expression of estrogen and progesterone receptors, the results of 46 ER+/PR+ women and 20 ER-/PR- women were selected as the object of the research. In 9 of the women with BC, distant metastasis of breast cancer was observed, and the results of these women were investigated as the metastatic BC group.

The aim of the research was to investigate parameters of diagnostic significance in the blood serum of women diagnosed with BC of various biological subtypes, to study the correlations between the obtained biochemical parameters and new markers, and to investigate HER-2 gene mutations in women with negative HER-2 expression in the local tissue.

Objectives of the research:

1.To carry out an intergroup comparative study of the levels of biochemical parameters, tumor markers and hormones in women with BC, including the HER-2-positive, HER-2-negative and triple-negative groups;

2.To comparatively study the blood serum levels of the matrix metalloproteinases MMP-7 and MMP-9 and of the cysteine-rich angiogenic protein (CYR-61) in women with BC and in the HER-2-positive, HER-2-negative and triple-negative groups formed according to HER-2 expression;

3.To carry out a comparative study of the levels of thyroid-stimulating hormone (TSH), prolactin, progesterone, estradiol, MMP-7, MMP-9 and CYR-61 in hormone receptor-positive (ER+/PR+) and hormone receptor-negative (ER-/PR-) women;

4.To comparatively study the blood serum levels of the matrix metalloproteinases MMP-7 and MMP-9 and of the CYR-61 protein in women with metastatic BC;

5.To evaluate the relationships between the studied parameters in women with BC by means of correlation analysis;

6.To evaluate the sensitivity and specificity of the studied parameters in women with BC by means of ROC analysis;

7.To investigate HER-2 gene mutations in women with HER-2-negative BC.

Research methods: The study included the results of 74 women diagnosed with BC of various biological subtypes and 15 practically healthy women of reproductive age. Breast biopsy materials of women with BC were examined, blood serum samples were obtained from all women included in the study, and serum parameters were analyzed by biochemical and enzyme immunoassay methods. In HER-2-negative women, mutations of this gene were investigated. The oncological patients included in the study were selected from among women who presented to the NOC MH RA and were diagnosed by an oncologist on the basis of anamnestic data and the results of clinical and laboratory analyses.

Biopsy specimens obtained from women with BC were examined by pathocytomorphological, immunohistochemical and genetic methods in the relevant laboratories of the NOC MH RA. Investigations of blood samples were performed at the Scientific Research Laboratory of the Department of Biological Chemistry of Azerbaijan Medical University. Serum levels of the matrix metalloproteinases (MMP-7 and MMP-9) and of CYR-61 were determined by the "Quantikine ELISA" method developed by "R&D Systems". Serum hormones were analyzed by enzyme-linked immunosorbent assay (ELISA) using reagent kits manufactured by "Diasino" (People's Republic of China), and measurements were performed on a Stat Fax 303+ (USA) microplate reader. HER-2 gene mutations were analyzed using "Amoy Dx" kits, and measurements were performed on a "Bio-Rad Real-Time PCR" system.

The main points of the dissertation for defense:

1.In women with BC, the levels of CEA, CA 15-3, ALT, AST, Ca^{2+}, vitamin D and CRP show significant changes compared with healthy women. In BC, the serum levels of the hormones prolactin, estradiol and progesterone change statistically significantly compared with healthy women. No statistically significant difference in TSH levels is found compared with healthy women.

2.In women with BC, an increase in CYR-61 levels and a decrease in MMP-9 levels are observed compared with the control group. In the intergroup comparison of the HER-2-positive, HER-2-negative and triple-negative (HER-2, ER, PR – negative) groups, the serum concentrations of the matrix metalloproteinases (MMP-7, MMP-9) and CYR-61 do not differ statistically significantly.

3.In BC, the serum levels of MMP-7, MMP-9 and CYR-61 do not differ between hormone receptor-positive (ER+/PR+) and hormone receptor-negative (ER-/PR-) women; among the studied parameters, a difference between these groups is found only in estradiol.

4.In women with metastatic breast cancer, CRP, MMP-9 and CA 15-3 can be applied as diagnostic markers compared with women without detected metastases;

5.In BC, negative correlations were found between CYR-61 and estradiol and MMP-9, and a positive correlation between MMP-9 and estradiol.

6.According to ROC analysis, the sensitivity and specificity of the biomarkers CEA, MMP-9 and CYR-61 in women with BC were rated as high.

7.In BC, the most common exon 18 and exon 20 mutations of the HER-2 gene are rarely encountered in cancer types with negative HER-2 expression.

Scientific novelty of the research. In this research, the main oncological markers involved in the development of various biological subtypes of breast cancer, the cell matrix proteins MMP-7 and MMP-9, the cysteine-rich protein CYR-61 and the regulatory hormonal status of the female organism were studied, and for the first time the mutual correlations between all obtained results were investigated. The degrees of sensitivity and specificity of the studied parameters were assessed using various statistical methods, and it was determined which of these parameters has the greatest diagnostic significance. For the first time in Azerbaijan, HER-2 gene mutations were investigated in women with BC with negative HER-2 expression.

Practical significance of the research. The obtained results

may help to clarify the molecular mechanisms of the processes occurring in various biological subtypes of breast cancer and to introduce new biochemical criteria into the early and differential diagnosis of breast cancer, as well as to support the prevention of the disease and the choice of treatment strategy. The study of tumor cell matrix proteins is of considerable scientific and practical importance for investigating the role of the cell matrix in the development and spread of breast cancer.

Approbation of the research. The materials of the dissertation were discussed at the republican scientific conference "Current problems of biology in the context of sustainable development" dedicated to the 100th anniversary of the National Leader of the Azerbaijani people Heydar Aliyev (Baku, 2023), the 2nd Azerbaijan International Laboratory Medicine Congress (Baku, 2024), the KBUD Congress & LAB EXPO 2024 National 12th Symposium on Laboratory Process Management (Antalya, 2024), the international scientific conference "AZLMC&LABEXPO The 3rd International Azerbaijan Laboratory Medicine Congress" (Baku, 2025), and the international conference "9th Cancer World Congress" (Prague, 2025). The preliminary discussion of the research results was held on 17 March 2026 at meeting No. 04 with the joint participation of the staff of the Departments of Biophysics and Biochemistry of Baku State University and the Department of Biological Chemistry of Azerbaijan Medical University. The seminar discussion of the dissertation was held on 3 November 2026 at the seminar meeting of the Dissertation council FD 2.31 operating at Baku State University (protocol No. 1).

Application of the research results in practice. The results of the dissertation are applied in the teaching process of the Department of Biological Chemistry of Azerbaijan Medical University.

Organization where the dissertation work was performed. The dissertation work was performed at the Department of Biophysics and Biochemistry of Baku State University. Laboratory investigations were carried out at the Department of Biological Chemistry of Azerbaijan Medical University and in the relevant laboratories of the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan.

Published works. Based on the results of the research, 8 scientific articles and 15 abstracts and conference materials have been published.

Volume and structure of the dissertation. The dissertation is written in Azerbaijani and consists of an introduction (15,159 characters), 4 chapters (Chapter I – 69,948 characters, Chapter II – 25,741 characters, Chapter III – 56,703 characters, Chapter IV – 32,153 characters), conclusions (3,194 characters), practical recommendations, a list of abbreviations and a bibliography of 201 sources, and is presented on 146 computer pages. The total volume of the dissertation (excluding figures, tables and the bibliography) is 200,053 characters. The dissertation contains 28 figures and 19 tables.

MATERIALS AND METHODS OF THE RESEARCH

The study included the clinical, pathohistological and laboratory results of 74 patients aged 32-61 years diagnosed with BC (main group). Based on the results of pathohistological examination, the women of the main group were divided into HER-2-positive, HER-2-negative and triple-negative (ER–, PR–, HER-2–) subgroups. The control group consisted of the results of 15 practically healthy women of reproductive age.

The study cohort consisted of women who presented to the NOC MH RA. The study groups were formed on the basis of the obtained patient data and various laboratory results, and investigations aimed at identifying new biomarkers were carried out on blood serum samples.

Various exclusion criteria were applied during the collection of study materials. Only women with a first-time diagnosis of BC were included in the main groups (HER-2-positive and HER-2-negative, triple-negative), and women with BC receiving chemotherapy or radiotherapy were excluded from the study.

Investigations of blood samples were performed at the Scientific Research Laboratory of the Department of Biological Chemistry of Azerbaijan Medical University.

Blood samples were taken from the cubital vein in the morning on an empty stomach from the practically healthy women and the

women with BC included in the study cohort. Part of the study was carried out on blood serum and plasma samples.

In women who presented to the National Oncology Center, complete blood count, biochemical parameters (ALT, AST, glucose, creatinine, CRP, Ca^{2+}, vitamin D) and serum levels of tumor markers were initially examined. Complete blood count was performed on a 3-part fully automated Sysmex "KX-21N" hematology analyzer (Germany), and biochemical analyses on "Erma AE-600N" (Japan) analyzers.

Serum concentrations of progesterone, estradiol, prolactin and TSH in all women of the study cohort were analyzed by ELISA using "Diasino" reagent kits.

Serum concentrations of MMP-7, MMP-9 and CYR-61 were determined by the Quantikine ELISA method using reagent kits manufactured by "Bio-Techne, R&D Systems" (USA).

All numerical data obtained in the course of the study were statistically analyzed in accordance with current recommendations. Parametric methods were used at the initial stage of statistical analysis. Statistical analysis was performed using variation, discriminant, correlation and ROC analysis methods.

All calculations were performed in "Microsoft Excel XP", in the EXCEL MS Office-2022 spreadsheet and in the SPSS-20 software package, and the results are presented in tables and diagrams.

RESULTS OF THE RESEARCH

Levels of biochemical parameters in women with breast cancer

In women with BC (n=74), the mean activities of the enzymes ALT and AST were 30.93±1.59 U/L and 29.59±1.7 U/L, respectively, which were 2.0-fold ($p<0.001$) and 1.7-fold ($p=0.004$) higher than in the control group (15.57±1.04 U/L and 18.13±1.21 U/L). The levels of calcium (2.35±0.01 mmol/L) and vitamin D (22.2±1.02 ng/mL) were 6% and 40.3% lower, respectively, than in the control group ($p<0.001$), whereas the CRP level (28.9±5.07 mg/L) was statistically

significantly higher (p=0.018). No statistically significant difference was found in creatinine and glucose levels.

In the groups formed according to HER-2 expression, AST activity in the HER-2-negative group (p=0.013) and vitamin D levels in the triple-negative group (p=0.030) were higher than in the HER-2-positive group. No differences in biochemical parameters were found between the hormone receptor-positive and -negative groups, while in women with metastatic BC the CRP level was higher than in the non-metastatic group (p=0.041).

Serum hormone levels in women with breast cancer

In women with BC, the prolactin level (18.9±1.3 ng/mL) was 1.6-fold higher than in healthy women (11.7±0.49 ng/mL) (p_U=0.006), whereas estradiol and progesterone levels were statistically significantly lower (p<0.001 and p=0.001, respectively). No difference in TSH levels (3.2±0.4 μIU/mL) was found compared with the control group (p_U=0.948).

In the HER-2-positive, HER-2-negative and triple-negative groups, the levels of prolactin, TSH and progesterone did not differ between the groups, whereas estradiol levels (18.5±1.6 pg/mL, 16.2±2.5 pg/mL and 32.0±13.2 pg/mL, respectively) differed statistically significantly between the groups (p=0.021). In the hormone receptor-negative group, the estradiol level (25.5±5.5 pg/mL) was higher than in the positive group (16.4±1.9 pg/mL) (p_U=0.004). In women with metastatic BC, no differences in hormone levels were found compared with the non-metastatic group.

Levels of tumor markers in women with breast cancer

In women with BC, the mean levels of the tumor markers CEA and CA 15-3 were 4.88±0.15 ng/mL and 48.6±6.2 U/mL, respectively, which were 2.5-fold (p<0.001) and 19.4-fold (p=0.001) higher than in the control group (1.92±0.19 ng/mL and 2.54±0.28 U/mL). The CEA level was higher in the HER-2-positive group than in the triple-negative group (p=0.015), while no differences in tumor marker

levels were found between the hormone receptor-positive and -negative groups. In women with metastatic BC, the CA 15-3 level (132.1±38.0 U/mL) was statistically significantly higher than in the non-metastatic group [$F(1;72)=37.062$; $p<0.001$].

According to correlation analysis, CEA correlates negatively with vitamin D, estradiol, progesterone, MMP-7 and MMP-9, and positively with CRP, CYR-61 and CA 15-3 ($\rho=0.521$; $p<0.001$); similar relationships were also found for CA 15-3. According to ROC analysis, the area under the curve (AUC) for CRP was 0.967±0.018 ($p<0.001$).

Levels of matrix metalloproteinases and CYR-61 in the blood serum of women with breast cancer

In order to evaluate the diagnostic significance of MMPs in women with BC, serum MMP-7 and MMP-9 levels were determined in the women included in the study. Matrix metalloproteinases belong to the extracellular endopeptidases and are capable of degrading all types of extracellular matrix proteins. These enzymes play an important role in tissue remodeling, cell proliferation and apoptosis, and are involved in the cleavage of membrane receptors and in the activation and suppression of chemokines and cytokines; to date, 28 types of MMPs have been identified in the human body. In recent years, the number of studies demonstrating increased expression of MMP-7 and MMP-9 in malignant tumor cells has been growing.

In the main group, the mean MMP-7 and MMP-9 levels were 4.50±0.87 ng/mL and 53.3±9.6 ng/mL, respectively. The minimum and maximum serum levels of MMP-7 and MMP-9 in women with BC ranged within 0.2–32.2 ng/mL and 8.0-688.0 ng/mL, respectively. This indicates considerable dispersion, particularly for MMP-9. In women with BC, the blood level of MMP-7 was 1.5-fold (46.6%) lower than in the control group ($p_F=0.464$) ($pU=0.014$), whereas the MMP-9 level was 9.1-fold (89.1%) higher (Table 1).

Table 1

MMP-7 and MMP-9 levels in women with breast cancer, Me (25%; 75%)

Groups / Parameters	Control (n=15)	Main group, women with breast cancer (n=74)
MMP-7, ng/mL	3.0 (2.5; 3.6)	1.4 (0.6; 3.8) p_U=0.014
MMP-9, ng/mL	371.0 (319.0; 705.7)	36.0 (24.0; 56.0) pt<0.001; pU<0.001

Note: p_t – according to Student's t-test with Bonferroni correction; p_U – according to the Wilcoxon test; p_F – statistical significance of the difference according to the ANOVA test.

Based on the analysis of median and quartile values, the median, Q1 and Q3 values of MMP-7 and MMP-9 in women with BC were Me 1.4 (0.6; 3.8) ng/mL and Me 218.0 (145.0; 341.0) ng/mL, respectively (Figure 1).

The results show a right-skewed asymmetry in the distribution of MMP-9. This may explain the discrepancy between the results of the parametric (F-test) and non-parametric (Mann–Whitney) tests. Thus, although no statistically significant difference was recorded for MMP-7 in the analysis of variance (p_F=0.464), the difference was significant in the non-parametric test (p_U=0.014). The heterogeneous distribution of these parameters may be explained by high variability in individual subgroups. According to the results of discriminant analysis in the studied group, the MMP-9 level differed statistically significantly from the control group (p_t<0.001) (pU<0.001) (Figure 2).

It should be noted that MMP-9 is one of the important proteolytic factors involved in basement membrane degradation and in stromal and vascular invasion. At the same time, the possibility that serum MMP-9 levels do not fully reflect local proteolytic activity in the tissue should be taken into account. The heterogeneity of serum MMP-7 levels may be explained by tumor stage, histological and molecular subtype (ER/PR/HER-2 status), and the metabolic and inflammatory background of the patient.

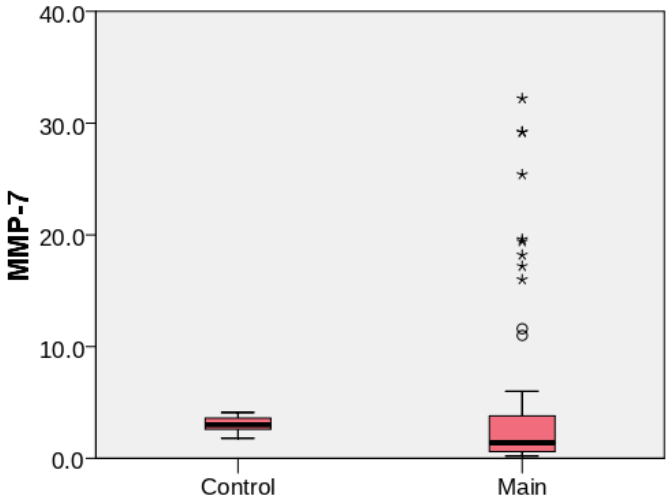


Figure 1. Comparative analysis of MMP-7 levels in women with breast cancer and in the control group

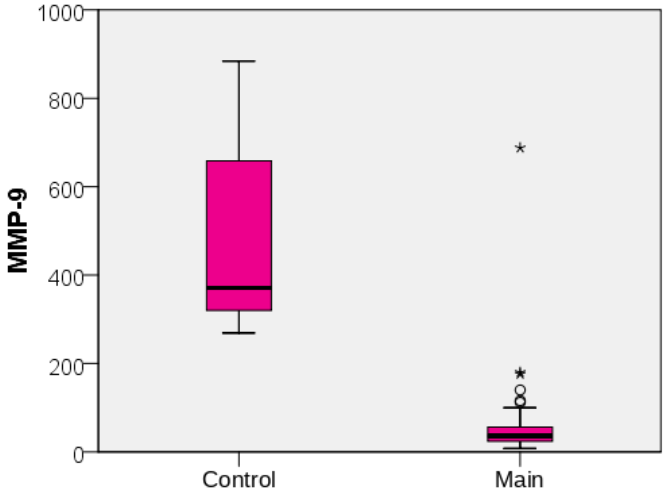


Figure 2. Comparative analysis of MMP-9 levels in women with breast cancer and in the control group

Thus, the results of the study show that determination of blood MMP-9 levels in women with BC may in the future be used as a diagnostic biomarker. The statistical analyses showed that MMP-7 is a less informative parameter in BC.

In order to determine the diagnostic significance of parameters associated with angiogenesis and tissue remodeling in women with BC, the blood level of the CYR-61 protein was investigated in the study groups.

In the main group, the serum level of CYR-61 protein did not differ statistically significantly from the results of the control group. In women with BC, CYR-61 levels ranged from 0 to 557.5 pg/mL, with a mean of 331.4±9.6 pg/mL. Although the CYR-61 level in this group was 24.9-fold higher than in the control group, no statistically significant difference (p_F=0.063) was found (Table 2, Figure 3).

CYR-61 is one of the regulatory secretory proteins involved in signal transduction across the extracellular membrane. Through integrins, it mediates cell attachment to the extracellular matrix and cell motility, and participates in the adhesion and migration of endothelial cells. An increase in its serum level may also be associated with the activation of stromal and endothelial cells.

Table 2

Blood CYR-61 levels in women with breast cancer, Me (25%; 75%)

Groups / Parameters	Control (n=15)	Main group, women with breast cancer (n=74)
CYR-61, pg/mL	0.0 (0.0; 12.0)	218 (145.0;341.0) p_t=1.000 p_U<0.001 p_F=0.063

Note: – significance of the difference compared with the control group, p_t – according to Student's t-test with Bonferroni correction; p_U – according to the Wilcoxon test; p_F – according to the ANOVA test.

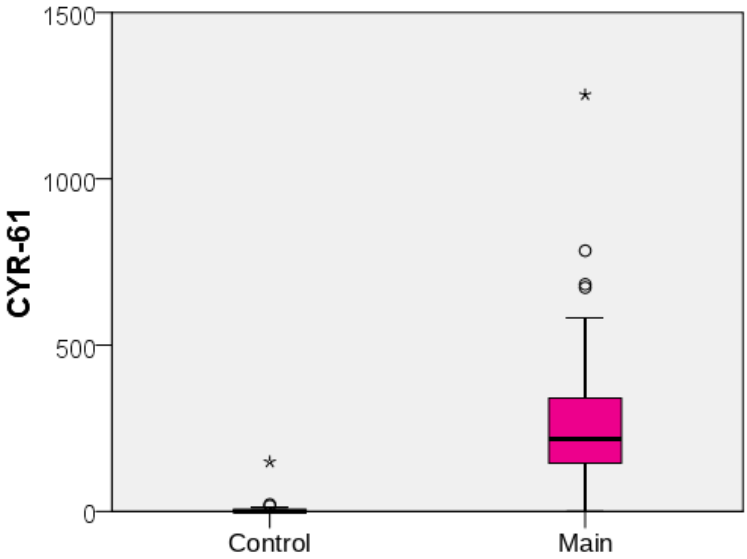


Figure 3. Comparative analysis of CYR-61 levels in women with breast cancer and in the control group

In women with BC, the median, Q1 and Q3 values of CYR-61 were Me 218.0 (145.0; 341.0) pg/mL. According to the results of discriminant analysis in this group, the CYR-61 level did not differ statistically significantly from the control group (p_t=1.000). Nevertheless, when changes in CYR-61 levels in this group were compared with the control group, the results of the Mann–Whitney test were statistically significant (p_U<0.001).

Thus, since the results of the Mann–Whitney test are taken as the basis for groups that do not follow a normal distribution, a marked increase in CYR-61 levels was observed in women with BC compared with healthy women, and the informative value of determining this parameter together with other parameters as a primary diagnostic marker was revealed. At the next stage, the investigation of the informative value of CYR-61 levels in individual groups will be continued.

Overall, the statistical evaluation of the analyses performed in women with BC showed that MMP-7, MMP-9 and CYR-61 levels in these women exhibit significant changes compared with healthy women.

Comparative study of MMP-7, MMP-9 and CYR-61 levels in women with HER-2-positive, HER-2-negative and triple-negative BC

Increased HER-2 expression is one of the factors promoting the rapid growth and division of tumor cells. Considering the involvement of extracellular matrix proteins in these processes, investigation of MMP-7 and MMP-9 levels in women with BC divided into groups according to HER-2 expression may be of diagnostic importance.

According to the comparative study of blood MMP-7 and MMP-9 levels in women with HER-2-positive BC, their mean values were 5.7±1.5 ng/mL and 37.5±4.4 ng/mL, respectively. In the HER-2-negative group these values were 3.0±0.9 ng/mL and 73.1±20.7 ng/mL, respectively, and in the triple-negative group 5.7±3.4 ng/mL and 37.0±7.5 ng/mL. The median values of the studied parameters are presented in Table 3 and Figure 4.

Table 3

Comparative study of serum MMP-7, MMP-9 and CYR-61 levels in women with HER-2-positive, HER-2-negative and triple-negative BC, Me (25%; 75%)

Groups / Parameters	HER2-positive n=33	HER2-negative n=33	Triple-negative (ER, PR, HER-2), n=8
MMP-7, ng/mL	1.2 (0.6; 4.8)	1.2 (0.8; 2.4)	2.0 (1.1; 4.9)
MMP-9, ng/mL	36.0 (24.0; 44.0)	40.0 (24.0; 76.0)	34.0 (20.0; 52.0)
CYR-61, pg/mL	187 (133; 341)	245 (166; 320)	199 (111.5; 303)

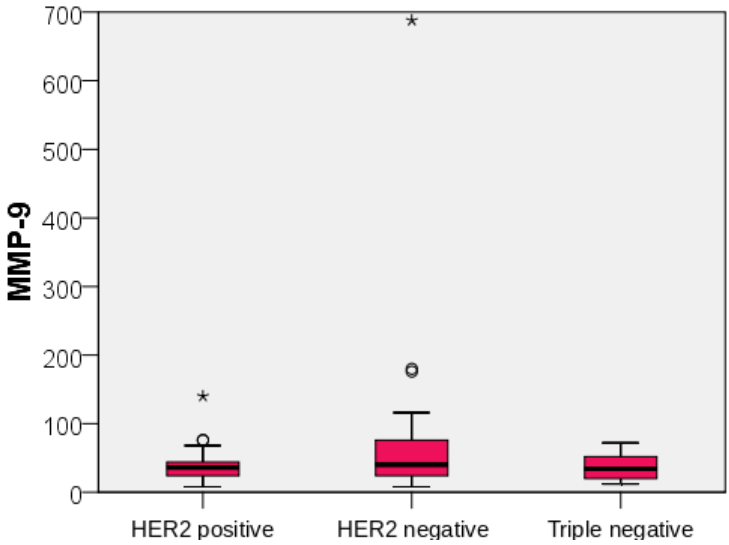


Figure 4. Comparative analysis of blood MMP-9 levels in the groups formed according to HER-2 expression

In women with HER-2-positive, HER-2-negative and triple-negative BC, the mean blood CYR-61 levels were 506.6±166.2 pg/mL, 277.5±31.3 pg/mL and 243.4±72.0 pg/mL, respectively. In all three groups, a statistically significant difference compared with the control group was observed (p_U<0.001). These results indicate that CYR-61 can be used as an additional diagnostic marker of BC and that its level is particularly high in the HER-2-positive subtype.

Comparative study of MMP-7, MMP-9 and CYR-61 levels in hormone receptor-negative and hormone receptor-positive women

Determination of serum MMP-7, MMP-9 and CYR-61 proteins in hormone receptor-negative women showed that their levels ranged within 0.2–32.2 ng/mL, 8.0–76.0 ng/mL and 0–683.0 pg/mL, respectively (Figures 5, 6, 7). In this group, the mean serum levels of MMP-7, MMP-9 and CYR-61 were 6.23±2.24 ng/mL, 33.6±4.2 ng/mL and 208.6±40.4 pg/mL, respectively. In the hormone

receptor-negative group, MMP-7 and CYR-61 levels were 2.0-fold ($p<0.001$) and 15.7-fold ($p<0.001$) higher, respectively, than in the control group, whereas the serum MMP-9 level was 14.5-fold lower ($p<0.001$).

In hormone receptor-positive women, serum levels of MMP-7, MMP-9 and CYR-61 ranged within 0.2-29.2 ng/mL, 8.0–688.0 ng/mL and 0-5575.0 pg/mL, respectively. In this group, the mean blood levels of MMP-7, MMP-9 and CYR-61 were 4.01±0.99 ng/mL, 63.6±15.0 ng/mL and 401.9±119.2 pg/mL, respectively. In the hormone receptor-positive group, MMP-7 and CYR-61 levels were 1.3-fold and 30.2-fold ($p<0.001$) higher, respectively, than in the control group, whereas the MMP-9 level was 7.7-fold lower ($p<0.001$).

According to the data, in hormone receptor-positive women the median value of MMP-7 was 1.2 ng/mL, with Q1 of 0.8 ng/mL and Q3 of 3.6 ng/mL. In this group, the median value of MMP-9 was 40.0 ng/mL (Q1 24.0 ng/mL and Q3 68.0 ng/mL), and the median value of CYR-61 was 243.0 pg/mL (Q1 166.0 pg/mL and Q3 341.0 pg/mL).

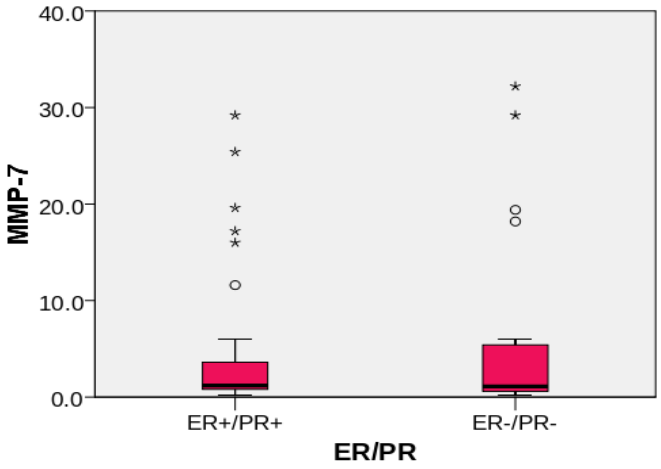


Figure 5. Comparative analysis of blood MMP-7 levels in hormone receptor-positive and -negative BC

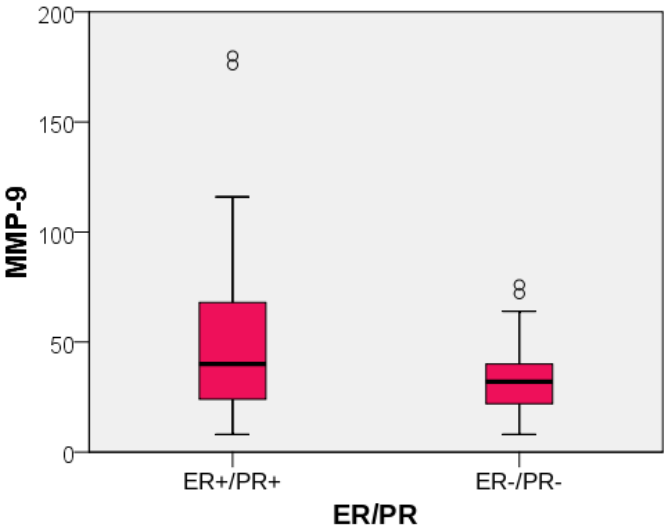


Figure 6. Comparative analysis of blood MMP-9 levels in hormone receptor-positive and -negative BC

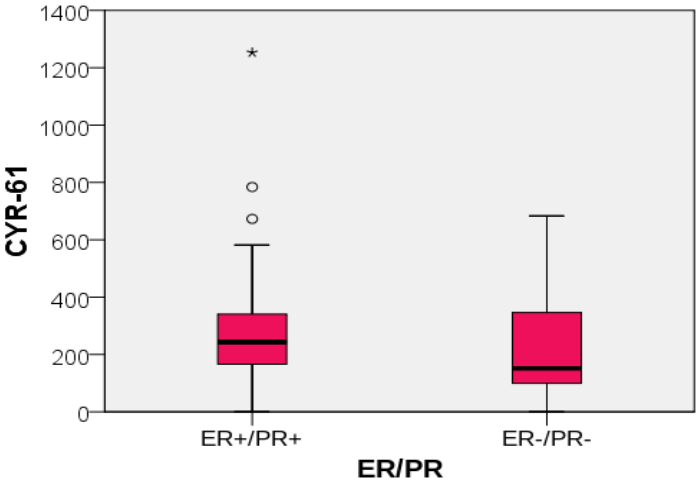


Figure 7. Blood CYR-61 levels in hormone receptor-positive and -negative BC

No statistically significant differences in MMP-7, MMP-9 and CYR-61 were found between the hormone receptor-positive and -negative groups. The median and Q1, Q3 quartile values of the serum levels of the studied proteins are presented in the table below (Table 4).

Table 4

Comparison of MMP-7, MMP-9 and CYR-61 levels in hormone receptor-negative and hormone receptor-positive women, Me (25%; 75%)

Groups / Parameters	Hormone receptor-negative BC, n=20	Hormone receptor-positive BC, n=46
MMP-7, ng/mL	1.1 (0.6; 5.4)	1.2 (0.8; 3.6) p=0.294
MMP-9, ng/mL	32.0 (22.0; 40.0)	40.0 (24.0; 68.0) p=0.198
CYR-61, pg/mL	151.5 (99.0; 346.5)	243.0 (166.0; 341.0) p=0.296

Note: p – statistical significance of the difference compared with the hormone receptor-negative group;

Thus, the absence of statistically significant differences between the groups divided according to hormone receptor status indicates that these blood parameters cannot be applied as primary diagnostic markers in this respect. Although MMP-9 and CYR-61 show significant differences from the control group in BC, their use cannot replace immunohistochemical methods performed on biopsy specimens in hormone receptor-positive or -negative cancers.

Comparative study of MMP-7, MMP-9 and CYR-61 levels in women with metastatic BC

Determination of blood MMP-7, MMP-9 and CYR-61 proteins in women with metastatic BC showed that their levels in this group

ranged within 0.4–4.8 ng/mL, 20.0–688.0 ng/mL and 99.0–784.0 pg/mL, respectively. In this group, the mean serum levels of MMP-7, MMP-9 and CYR-61 were 1.91±0.45 ng/mL, 122.7±71.7 ng/mL and 332.1±79.4 pg/mL, respectively (Figures 8-10).

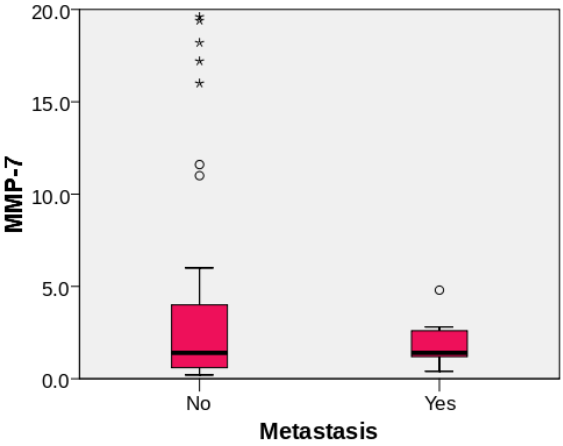


Figure 8. Comparative analysis of blood MMP-7 levels in women with metastatic BC

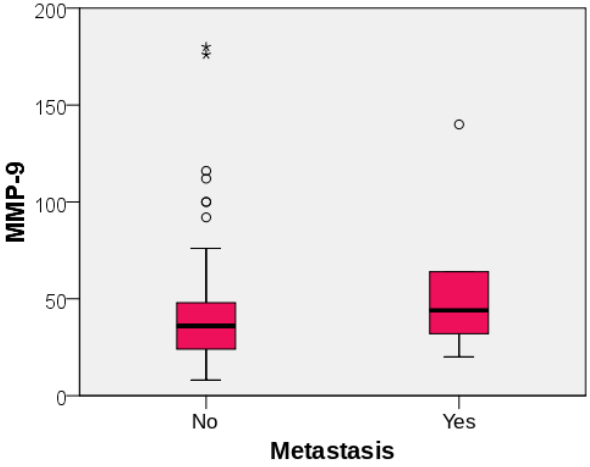


Figure 9. Comparative analysis of serum MMP-9 levels in women with metastatic BC

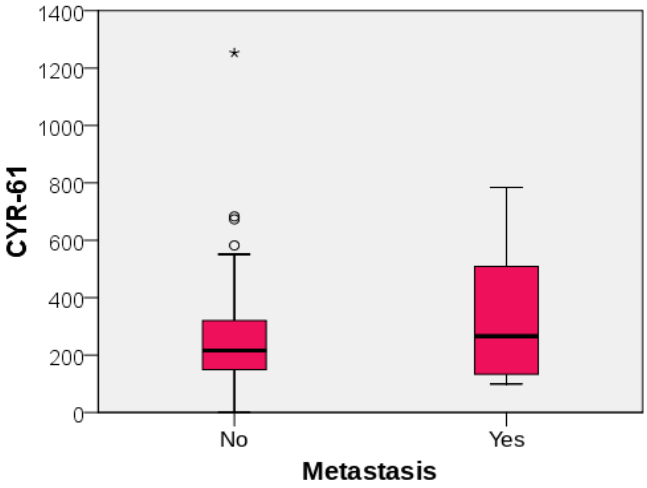


Figure 10. Comparative analysis of blood CYR-61 levels in women with metastatic BC

According to the results of the study, the median MMP-7 level in women with metastatic BC was 1.4 ng/mL (1.2; 2.6).

In women with metastatic BC, the median MMP-9 level was 44.0 ng/mL (32.0; 64.0). In the metastatic BC group, the median CYR-61 level was 266.0 pg/mL, ranging between 133.0 pg/mL (Q1) and 509.0 pg/mL (Q3) (Table 5).

Table 5

Comparative study of MMP-7, MMP-9 and CYR-61 levels in women with metastatic BC, Me (25%; 75%)

Groups / Parameters	Non-metastatic BC (n=65)	Metastatic BC, (n=9)
MMP-7, ng/mL	1.4 (0.6; 4.0)	1.4 (1.2; 2.6)
MMP-9, ng/mL	36.0 (24.0; 48.0)	44.0 (32.0; 64.0), p_t=0.006
CYR-61, pg/mL	216.0 (149.0; 320.0)	266.0 (133.0; 509.0)

Note: p_t – statistical significance of the difference compared with the non-metastatic BC group according to Student's t-test with Bonferroni correction

According to the statistical analysis of the obtained results, a statistically significant difference between the metastatic and non-metastatic groups was found only in MMP-9 levels [F(1;72)=7.89; p=0.006].

Thus, the results of the statistical analyses showed that in women with metastatic BC, CRP, CA 15-3 and MMP-9 levels increase statistically significantly compared with the non-metastatic group. These changes indicate that the metastatic process is associated with both molecular-invasive and systemic inflammatory mechanisms.

The increase in MMP-9 levels in metastatic BC may be explained by the degradation of extracellular matrix components, destruction of the basement membrane and the creation of favorable conditions for vascular invasion by tumor cells.

Investigation of correlations between the studied parameters in women with breast cancer and determination of sensitivity and specificity using ROC curves

Correlation analysis revealed that in women with BC there is a correlative dependence between the parameters determined for the first time and other biochemical parameters. Thus, according to the results of the study, correlations were observed between MMP-7 and estradiol (ρ=0.217, p=0.041), and between MMP-9 and estradiol (ρ=0.329, p=0.002), progesterone (ρ=0.425, p<0.001) and CYR-61 (ρ=-0.314, p=0.003).

The results suggest that the weak positive correlation identified between MMP-7 and estradiol may reflect the influence of estrogen receptor activity in the pericellular microenvironment of tumor tissue on proteolytic activity. It is known that estrogen receptor-mediated signaling, in addition to stimulating cell proliferation, can also induce gene expression of matrix metalloproteinases. In this respect, changes in estradiol levels may enhance tumor cell invasiveness by increasing MMP-7 expression.

The moderate positive correlation identified between MMP-9 and estradiol indicates that estrogen may play a role in the regulation of MMP-9 levels. MMP-9 is known to be one of the factors involved

in cell invasion and angiogenesis. The estrogen signaling system can stimulate activation of the MMP-9 gene, which in turn may accelerate metastatic processes by enhancing degradation of the basement membrane and extracellular matrix components.

The positive correlation observed between MMP-9 and progesterone suggests that the progesterone signaling system modulates proliferative and invasive processes.

One of the most notable findings is the negative correlation identified between MMP-9 and CYR-61. CYR-61 is a cell matrix protein involved in cell adhesion, proliferation and angiogenesis around tumor cells. The increase in MMP-9 in metastatic cancer accompanied by a decrease in CYR-61 levels may be explained by compensatory mechanisms against the background of extracellular matrix destruction and disruption of intercellular contacts.

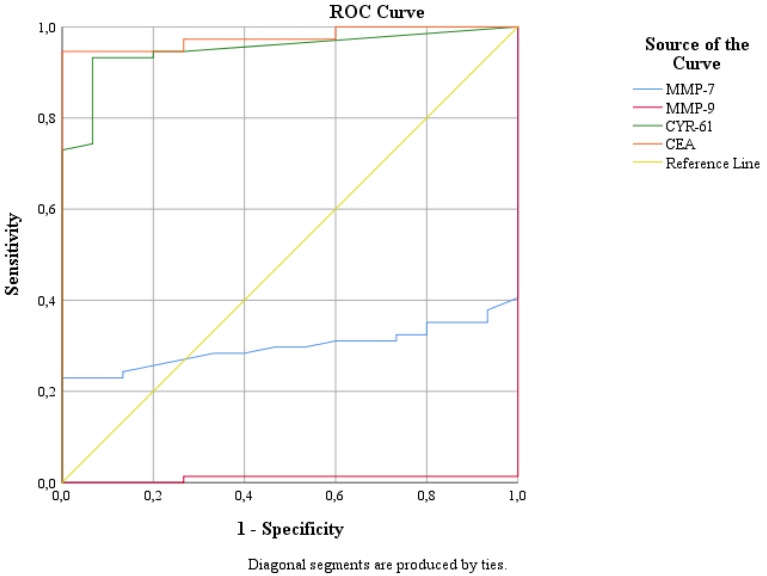
Overall, the identified correlations indicate the existence of functional interactions between hormonal factors and MMPs.

To determine the sensitivity and specificity of the studied parameters, their ROC (Receiver Operating Characteristic) curves were constructed. ROC analysis reflects the diagnostic significance of the investigated parameters. The numerical value of the curves obtained by ROC analysis is assessed by the area under the curve (AUC). In the ROC curve, sensitivity is plotted on the ordinate and specificity (as 1 – specificity) on the abscissa. If the area under the curve lies between 0.5 and 1.0, the test is considered diagnostically significant. The closer the result is to 1.0, the higher the discriminatory power of the test between diseased and healthy individuals. If the AUC is statistically significant ($p<0.05$), this indicates the potential usefulness of the parameter in the diagnosis of the disease.

Based on the ROC curve, it was determined that among the biochemical parameters the area under the curve for CRP was 0.967±0.018, with the lower and upper limits of the 95% confidence interval being 0.932 and 1.000, respectively ($p<0.001$).

The ROC curve for prolactin in women with BC showed that the area under the curve was 0.727±0.050, with the lower and upper limits of the 95% confidence interval being 0.629 and 0.826, respectively (Graph 3.6.2).

The area under the ROC curve for CEA of 0.977±0.014 indicates its high diagnostic significance (p<0.001). The low standard error confirms the stability of the result (Graph 1).



Test result variable(s)	Area under the curve	Standard error	P (significance)	95% confidence interval	
				Lower bound	Upper bound
MMP-7	0.298	0.051	0.014	0.197	0.398
MMP-9	0.010	0.010	0.000	0.000	0.030
CYR-61	0.950	0.024	0.000	0.903	0.997
CEA	0.977	0.014	0.000	0.949	1.000

Graph 1. Evaluation of the sensitivity and specificity of MMP-7, MMP-9, CYR-61 and CEA in women with breast cancer by ROC analysis

Thus, based on the results of correlation and ROC analyses, it can be stated that in breast cancer it is important to study MMP-7, MMP-9 and CYR-61 levels along with hormones, CRP and tumor

markers. CYR-61 and MMP-9 are biomarkers with high specificity and sensitivity in the diagnosis of BC.

Investigation of *HER-2* gene mutations in women with HER-2-negative breast cancer

One of the main objectives of the study was to investigate somatic mutations in the *HER-2* gene in women with HER-2-negative BC. For this purpose, materials obtained from the breast tissue of 23 HER-2-negative women were collected. HER-2 gene mutations in paraffin-embedded breast tissue samples were analyzed by the author at the molecular oncology laboratory of the NOC MH RA. For this purpose, sections were prepared from FFPE blocks using a microtome, and deparaffinization was carried out in accordance with the manufacturer's protocol.

Genomic DNA was isolated using the "One-4-All Genomic DNA" kit manufactured by Bio Basic. During DNA extraction, the incubation steps were optimized taking into account the fragmentation characteristics specific to breast tissue. After purification performed at least 5 times, DNA concentration and purity were assessed spectrophotometrically. Samples with an A260/A280 ratio within 1.8–2.0 and a concentration of not less than 20 ng/μL were considered suitable for amplification and included in the study.

HER-2 gene mutations were detected by real-time PCR using the "HER-2 Mutation Detection" kit of "AmoyDx". The study was carried out step by step in accordance with the manufacturer's instructions. Specific fluorescent signals during amplification were recorded on a semi-automated Bio-Rad real-time PCR system. The study was aimed at identifying clinically significant point mutations located in the tyrosine kinase domain of the HER-2 gene.

According to the results of the molecular genetic analyses, no mutations in the *HER-2* gene were detected in tissue samples from 33 women with negative HER-2 expression. The positive and negative control samples yielded the expected results, confirming that the genetic procedures were technically performed correctly.

Thus, according to the results of the investigation of HER-2 gene

mutations in the studied group, the mutation frequency was 0%. This suggests that HER-2 mutations are rarely encountered in cancer types with negative HER-2 expression in women with BC. Considering that the obtained results relate to 33 patients, the limited sample size reduces the probability of detecting HER-2 mutations and, in this respect, increases the need to conduct such studies in larger populations.

CONCLUSIONS

1. In women with BC, the levels of CEA ($p<0.001$), CA 15-3 ($p=0.001$), Ca^{2+} ($p<0.001$), vitamin D ($p<0.001$) and CRP ($p=0.018$) show significant changes compared with healthy women; in BC, the serum levels of the hormones prolactin ($p=0.018$), estradiol ($p<0.001$) and progesterone ($p=0.001$) change significantly compared with healthy women, while no statistically significant difference in TSH levels is found compared with healthy women.

2. In women with BC, an increase in CYR-61 levels and a decrease in MMP-9 levels ($p<0.001$) are observed compared with the control group; in the HER-2-positive, HER-2-negative and triple-negative (HER-2, ER, PR negative) groups, the serum concentrations of the matrix metalloproteinases (MMP-7, MMP-9) and CYR-61 do not differ statistically significantly compared with the control group.

3. In breast cancer, the serum levels of MMP-7, MMP-9 and CYR-61 do not differ between hormone receptor-positive (ER+/PR+) and hormone receptor-negative (ER-/PR-) women; among the studied parameters, an intergroup difference is found only in estradiol levels.

4. In women with metastatic BC, CRP, MMP-9 and CA 15-3 increase statistically significantly compared with non-metastatic BC. According to the results of the analysis of variance, the MMP-9 level in the metastatic BC group was statistically significantly higher than in the non-metastatic group [$F(1;72)=7.89$; $p=0.006$]. This may be explained by the involvement of MMP-9 in extracellular matrix degradation and tumor cell invasion.

5. In women with BC, correlations are observed between MMP-7 and estradiol (ρ=0.217, p=0.041), and between MMP-9 and estradiol (ρ=0.329, p=0.002), progesterone (ρ=0.425, p<0.001) and CYR-61 (ρ=-0.314, p=0.003). At the same time, CEA correlates negatively with vitamin D (ρ=-0.462, p<0.001), estradiol (ρ=-0.365, p<0.001), progesterone (ρ=-0.440, p<0.001), MMP-7 (ρ=-0.257, p=0.015) and MMP-9 (ρ=-0.472, p<0.001), and positively with CRP (ρ=0.285, p=0.007), CYR-61 (ρ=0.307, p=0.003) and CA 15-3 (ρ=0.521, p<0.001). Similar correlations are also found for CA 15-3.

6. According to ROC analysis, the sensitivity and specificity of the biomarkers CEA, MMP-9 and CYR-61 in women with BC were rated as high.

7. In women with breast cancer, the A775_G776insYVMA, M774_A775insAYVM, G776>VC, G776R, G776C, P780_Y781insGSP and V777L mutations located in exons 18 and 20 of the HER-2 gene are rarely encountered in cancer types with negative HER-2 expression.

PRACTICAL RECOMMENDATIONS

1. Given the high informative and diagnostic value of MMP-9 in the diagnosis of metastatic breast cancer, its determination is recommended for the early detection of the disease.

2. To assess the pathological aspects of the disease in women with breast cancer, determination of CYR-61 concentration together with other parameters is recommended in primary diagnosis.

3. Biomarkers such as CYR-61 and MMP-9 have great potential for monitoring cancer progression. Their use in clinical practice may help to obtain more accurate results in disease monitoring. In particular, regular assessment of these biomarkers by blood tests may ensure diagnosis and follow-up of treatment by less invasive methods.

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LIST OF ABBREVIATIONS

ALT – alanine aminotransferase
ANOVA – analysis of variance
AST – aspartate aminotransferase
AUC – area under the ROC curve
BC – breast cancer
CA 15-3 – cancer antigen 15-3
CEA – carcinoembryonic antigen
CRP – C-reactive protein
CYR-61 – cysteine-rich angiogenic inducer 61
DNA – deoxyribonucleic acid
ELISA – enzyme-linked immunosorbent assay
ER – estrogen receptor
HER-2 – human epidermal growth factor receptor 2
IL – interleukin
Me – median
MMP – matrix metalloproteinase
NK – natural killer cells
NOC MH RA – National Oncology Center of the Ministry of Health of the Republic of Azerbaijan
PCR – polymerase chain reaction
PR – progesterone receptor
ROC – Receiver Operating Characteristic
STAT – signal transducers and activators of transcription
TMB – tetramethylbenzidine
TNF-α – tumor necrosis factor-α
TSH – thyroid-stimulating hormone
WHO – World Health Organization

The defense will be held on 18 . 12 . 2026 at 11.00 at the meeting of the Dissertation council FD 2.31 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Baku State University.

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