SIGNIFICANCE OF SERUM BIOMARKERS FOR BREAST CANCER

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KO‘KRAK BEZI SARATONI UCHUN ZARDOB BIOMARKERLARINING AHAMIYATI

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ЗНАЧЕНИЕ СЫВОРОТОЧНЫХ БИОМАРКЕРОВ ДЛЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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Abstract. *Tumor biomarkers are produced in the body by tumor cells or other cells. They are responsible for the presence of the cancer conditions. Many tissue and plasma biomolecules are responsible for breast cancer; we discuss some of these in this article. These biomarkers are important in breast cancer diagnosis, analysis of treatment results, early detection of metastases, and disease recurrence. In this literature review, we analyze the results of studies on the significance of certain serum markers for breast cancer.*

Keywords: *breast cancer, serum biomarkers, biomarkers, patient survival, interleukin, CA-15.3.*

Annotatsiya. *O‘sma biomarkerlari organizmda turli hujayralar, jumladan o‘sma hujayralarining o‘zida ham ishlab chiqariladi. Mazkur biomarkerlar saraton uchun javobgar hisoblanadi. Biz maqolada ulardan ba’zilarini muhokama qilamiz. Ushbu biomarkerlar ko‘krak bezi saratoni diagnostikasida, davolash natijalarini tahlil qilishda, metastazlarni erta aniqlashda va kasallikning qaytalanishini baholashda muhim hisoblanadi. Ushbu adabiyotlar sharhida ayrim zardob markerlarining ko‘krak bezi saratoni uchun ahamiyati haqida tadqiqotlar natijalarini tahlil qilamiz.*

Kalit so‘zlar: *ko‘krak qafasi, zardob biomarkerlari, bemorlar yashovchanligi, interleykin, CA-15.3*

Аннотация. *Опухолевые биомаркеры производятся в организме опухолевыми или другими клетками. Они несут ответственность за наличие раковых заболеваний. Многие биомолекулы тканей и плазмы ответственны за рак молочной железы, мы в этой статье обсуждаем некоторые из них. Эти биомаркеры важны для диагностики рака молочной железы, анализа результатов лечения, раннего выявления метастазов и рецидивов заболевания. В обзоре литературы мы анализируем результаты исследований значимости некоторых сывороточных маркеров рака молочной железы.*

Ключевые слова: *рак молочной железы, сывороточные биомаркеры, биомаркеры, выживаемость пациентов, интерлейкин, CA-15.3.*

Introduction. Breast cancer is a heterogeneous disease, the most common among women, and causes their death. Early diagnosing breast cancer and detecting metastases in the early stages is essential for proper and effective treatment. Biomarkers are the most critical tools in disease management. Their role is incomparable in early diagnosis, monitoring of treatment results, early detection of disease recurrence and metastases, and predicting survival. Many clinical and pathological characteristics of the cancer, such as the clinical stage of the disease,

tumor size, spread to lymph nodes, and HER2/neu expression, are considered when predicting breast cancer. Among the classical biomarkers, ER, PR, HER2, exosomes, Ki-67, miRNAs, and many other protein biomarkers have been used to diagnose BC; however, these biomarkers show limitations due to the heterogeneity of tumors and the inaccuracy of clinical evidence linked with multifactorial aspects of the disease. In recent years, molecular oncology has developed, and researchers have discovered the predictive value of many tissue and plasma biomarkers for cancer. In 2005, the European Tumor Markers Group set guidelines for using biomarkers for breast cancer. [1] Since then, predictive biomarkers have been conducted in many studies. [2] Numerous tissue markers currently are used in breast cancer management. However serum biomarkers are not as established for management of breast cancer. We will review the circulating biomarkers CA 15.3, CEA, TPSA and discuss some non-specific serum markers IL-6, TNF-alpha, VGFR and EGFR.

Ca-15.3. Ca-15-3 soluble protein is one of the representatives of the MUC-1 (epithelial membrane antigen) family and is the most widely used among breast cancer prognostic markers. CA-15.3 expression is on the surface of various epithelial cells. Its high expression is in breast cancer in 90% of cases. [3] The specificity of CA15.3 for breast cancer is 91.2%, and the sensitivity is 61.1%. [4] In early-stage breast cancer, scientists can determine the presence or absence of micrometastases throughout the body by measuring the amount of CA-15.3 before surgery. Duffy et al. [5] found that elevated serum CA-15.3 (25≤U/ml) in 585 women was a predictor of poor disease outcome and decreased median overall and disease-free survival. CA-15.3 is also influential in assessing tumor response and determining the effectiveness of chemotherapy. Researchers studied the predictive capabilities of CA-15.3 and CEA in early and late-stage breast cancer for monitoring adjuvant chemotherapy in Jordanian women, and they concluded that CA-15.3 is more effective than CEA in late-stage cancer. [3] Indian scientists analyzed the predictive potential of CA 15-3 in the blood of patients before treatment, after completion of treatment, and after six months. Most patients had high levels of the biomarker before treatment, and only a minority had elevated blood levels of CA15-3 after treatment. Scientists found a correlation between changes in the amount of CA-15.3 before treatment and six months later and concluded that it depends on the histological type and size of the tumor. [6] Researchers achieved good results with CA15.3 in assessing overall and disease-free survival when patients were monitored for blood biomarkers post-treatment (surgery or chemotherapy) until death. [7] The sensitivity of CA15.3 in the early detection of tumor spread in the body is 46%. [8] In some studies, it is 82.1%. [9] CA-15.3 content is incredibly high in bone metastases compared to metastases in other organs. [9] In conclusion, CA15.3 is a prognostic biomarker in early-stage breast cancer, but there is no significant difference in plasma levels between early breast cancer and healthy women. Therefore, CA-15.3 is useless for use in screening programs. Combined use with other diagnostic and prognostic methods is highly effective. [7]

CEA. It is one of the critical plasma biomarkers for breast cancer and many other types of cancer. Human cancer-embryonic antigen has been fully characterized and consists of 29 genes. Eighteen are expressed - 7 belong to the cancer-embryonic antigen subgroup, and 11 belong to the pregnancy-specific glycoprotein subgroup. This antigen is used in the clinic to diagnose many cancers. Cancer embryonic antigen, produced in the intestinal cells of a healthy person, passes from the apical part of the columnar cells to the intestinal cavity and leaves the body together with the feces. A small amount of CEA can be in a healthy person's blood. As cancer cells lose their polarity, the synthesized CEA begins to accumulate around these cells. Later, it drains into the blood and lymph vessels, and its amount in the blood increases. As the size of the tumor grows, the amount of CEA increases as well. [10]

CEA cannot used for screening diagnostic purposes in early-stage breast cancer. There is no significant difference in its amount in serum for benign tumors and early-stage cancer. [10, 11] In predicting breast cancer, determining the amount of CEA in serum and traditional prognostic criteria gives a good result. Determination of the amount

of CEA in plasma before surgical procedures indicates the presence of micrometastases in the body. When the amount of CEA increases to 7.5ng/ml, it is possible to consider the presence of micrometastases in the body. [11] Uygur et al. [9] studied the relationship between the clinical and morphological signs of breast cancer and the amount of CEA in the blood. According to research findings, the amount of REA in the blood is higher in postmenopausal patients, lobular cancer, hormone receptor-positive and HER2/neu receptor-negative cancer. Several studies that investigated CEA as a predictor confirmed it as an independent predictive marker for breast cancer diagnosis at an early stage and preoperative conditions. [12, 13]

TPSA. The proliferation rate of tumor cells is one of the crucial phenotypes that indicate the aggressiveness of the process and is a critical aspect to evaluate in predicting the progression and outcome of the disease. [14] Cytokeratins are serological markers to assess tumor proliferation in several epithelial carcinomas, such as breast, lung, colon, and gallbladder cancer. [15] Cytokeratins are a measuring criterion of tumor proliferative activity. Tissue polypeptide specific antigen (TPSA) is one of the cytokeratins; the amount in the blood is 1-75 ed/l. [16] According to the study results, TPS has a higher sensitivity than other biomarkers in monitoring the chemotherapy process in breast cancer. When the size of the tumor decreases, the amount of TPS decreases rapidly, and on the contrary, when the size of the tumor increases, its amount in the blood rises quickly. [17] Also, TPS correlates with disease stage and grade. That is, TPS increases significantly from stage I to stage IV. Preoperative measurement of TPS can be used as an independent biomarker to predict disease-free or overall survival. [16] However, the amount of TPS is high in the presence of other inflammatory processes, such as liver damage or during ovulation. [18-19] At the same time, it is relatively high in postmenopausal women. [20] Recent research findings prove that TPS can be used to detect early-stage breast cancer and show that the sensitivity of this biomarker is higher than conventional CA15-3 and CEA. [21]In clinical practice, it is practical to use TPS to predict tumor response to chemotherapy, depending on the preoperative serum levels.

IL-6. Cytokines are small molecular (15-20 kDa) and short-lived proteins that are essential in transmitting intercellular and intracellular signals. [22] Cytokines divide into different families according to their receptor structure, composition, and specific characteristics. [23] Among them, representatives of the IL-6 family are important cytokines affecting the process of carcinogenesis. Representatives of the family: IL-6, IL-11, IL-27, oncostatin-M (OSM), cardiotropin-1, cardiotropin-like cytokine, leukemia inhibitory factor (LIO), ciliary neurotrophic factor, and in recent years, addition to this family added IL-35 and IL-39. [24] Human IL-6 glycoprotein consists of 185 amino acid residues.[25] This multifunctional interleukin participates in metabolism, immune responses, inflammation, hematopoiesis, bone tissue formation, and carcinogenesis. [26] IL-6 is a cancer-causing factor that causes obesity and chronic inflammation. In 20% of cancer cases, there is chronic inflammation and pain with regular infectious diseases at the basis of the disease. In the remaining cases, even if there is no chronic inflammation at the basis of cancer development, later infiltration occurs due to cancer in the body. Il-6 not only causes cancer-related inflammation but also participates in the repair of damaged DNA fragments, antioxidant defense system, proliferation, invasion, metastasis, and angiogenesis. [27] In prostate cancer, breast cancer, myeloma, hepatocellular cancer, and many other types of cancer, a high concentration of IL-6 in the blood plasma means a poor prognosis of the disease. [28] There is a correlation between the amount of IL-6 in the blood and the tumor size. Il-6 can be used in practice as a tumor biomarker predicting disease recurrence. Tripsianis at al. [29] concluded that IL-6 can be an independent predictor for breast cancer. Accordingly, a high concentration of il-6 in the blood plasma predicts the spread of the process to the lymph nodes and short survival. In primary breast cancer, IL-6 is not only a predictor but also has therapeutic value, with IL-6 expression underpinning the development of resistance in patients to trastuzumab, tamoxifen, and paclitaxel. [30-32] Approximately 70% of patients with breast cancer have positive

estrogen/progesterone receptors and accepted antiestrogen therapy. [33] However, 50% of tamoxifen patients occure disease recurrence. [34] In this setting, patients with tamoxifen resistance showed higher expression of IL-6 and decreased overall survival. In vitro and in vivo studies have shown that target therapy with IL-6R with Tocilizumab, reducing its expression, reduces tamoxifen resistance in patients. [31] Even in HER2/neu positive patients with advanced resistance to trastuzumab, IL-6R antibody or blocking the IL-6/STAT3 signaling pathway reduced IL-6R-induced inflammation. As a result, tumor growth and metastases are prevented due to the reduction of the tumor cell population. [30] Block of the IL6-R/STAT-3 signaling pathway in cultured breast cancer cells slowed the proliferation, invasion, and migration processes. [35] In conclusion, IL-6 affects the pathophysiology of breast cancer. Although there is sufficient evidence that IL-6 can cause breast cancer, there are many studies on its involvement in the disease's progression, metastasis, and recurrence. Therefore, a high level of IL-6 in the serum predicts a poor disease outcome.

TNF-alpha. TNF alpha is one of the essential inflammatory cytokines, part of the tumor microenvironment, and produced by stromal cells, macrophages, and tumor cells. [36] First identified in 1975, TNF-alpha has been studied to induce tumor hemorrhagic necrosis and is the most promising cytokine for cancer therapy. [37] However, recent studies have shown this cytokine is a chronic inflammatory and tumor-promoting agent. [36] Many scientists studied TNF-alpha as a predictive marker for breast cancer. TNF-alpha in blood plasma is higher in cancer patients than in healthy people. Its amount in blood correlates with some clinical and pathomorphological characteristics of cancer. For example, disease stage, tumor size, spread to lymph nodes. In invasive breast cancer, the tumor size is 5 cm or more, or when the process has spread to the lymph nodes, the amount of TNF in the blood is high. It can be an effective parameter in evaluating disease stage and severity. [38] In locally advanced breast cancer, the level of TNF-α can be a marker predicting the clinical response of the tumor to neoadjuvant chemotherapy. [39] During treatment with anthracyclines, an excessively high level of TNF alpha causes DNA fragmentation of tumor cells, resulting in resistance to doxorubicin. At the same time, glutathione controls the S transferase molecule. Due to the expression of TNF, this enzyme causes detoxification of doxorubicin, and its cytotoxic effect on breast cancer cells disappears. [40] Elevating this cytokine may independently predict disease-free or short overall survival in patients. [29] Also, Perez-Tejada at al. [41] studied cytokines' role in assessing breast cancer survivors' quality of life. TNF-alpha levels are higher in women who are persistently depressed, lonely, and have a low quality of life. It can be the basis for developing new strategies to increase the survival rate of women who survive the disease by improving the quality of life style.

VGFR. Angiogenesis is a complex process that takes place under the influence of pro-angiogenesis and angiogenesis inhibitors, and it takes place with the participation of VEGF. Members of the VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-F, PGF) are secreted glycoproteins with a molecular mass of about 40 kDa. [42] In the embryonic period, VEGF forms new vessels with the differentiation of endothelial cells from hemangioblasts. The postnatal period, physiological (restoration of cut vessels, menstrual cycle, formation of the blood circulation system between mother and child during pregnancy) and pathological (tumor growth), metastasis, diabetic retinopathy, ischemia, etc.) is involved in the processes. [42] In 1971, Folkman proposed that tumor progression and growth are due to angiogenesis and that antiangiogenic drugs effectively treat cancer. [42, 43] In 1983, Senger identified a protein that increases vascular permeability synthesized in animal cancer cells. In 1989, Ferrara [43] independently described the role of VEGF in angiogenesis. After that, the role of angiogenesis in carcinogenesis was found to be necessary, and an antiVEGR monoclonal antibody was discovered. Currently, this monoclonal antibody (AVASTIN) is used in target therapy to treat colon, lung, and breast cancer. [42, 43] Cancer cells may develop resistance after long-term antiangiogenic therapy. In an experiment conducted by Casanova et al. [44] resistance

to long-term antiangiogenic therapy occurs due to the expression of receptors for angiogenesis factors other than VEGF. They affected mouse cancer cells by 2-fold stress, i.e., hypoxia and reduced blood nutrition, but after ten repeated cycles, cancer cells increased invasiveness and showed high viability.

Blood levels are significantly higher in breast cancer and ER-positive breast cancer than in other cancers. [45] In another study, high blood and tissue VEGF concentrations correlated with tumor stage, size, lymph node involvement, negative hormone receptor negativity, HER2/neu positivity, and poor prognosis. [44]As can be concluded from the above, VEGF is an essential marker for the diagnosis and treatment of breast cancer and for predicting the disease's outcome.

EGFR. The epidermal growth factor receptor belongs to the EGFR family and is abundantly located on the surface of mammalian epithelial cells. The EGFR family consists of EGFR (ErbB1 or HER1), HER2 (HER2/neu or ErbB2), ErbB3 (HER3), and ErbB4 (HER4). [46] The results of recent studies show the essential physiological involvement of EGFR in embryonic and postnatal development. It also plays an important pathogenetic role in the development of many tumors and is a factor strongly affecting the poor outcome of the disease in cancer patients. In recent years, a lot of research has been conducted in molecular oncology to target specific molecules that increase tumor growth and viability. HER2 is the most important representative of EGFR family members in target therapy, and it has high expression in 20-25% of breast cancers. High levels of these molecular biomarkers indicate a poor prognosis of the disease. Increased serum levels of EGFR are observed in infiltrative breast cancer and triple-negative breast cancer with a poor outcome. [46] EGFR expression is in 30% of infiltrative breast cancer and 50% of cases of triple negative subtype. [47-48] In breast cancer, EGFR receptor expression is observed in 20-80% of cases, leading to uncontrolled tumor growth. [48] Turkish scientists Tas at al. [49] found that the amount of EGFR in blood plasma is higher in cancer patients than in healthy people. Plasma EGFR levels are significantly higher in healthy individuals than in cancer patients. When the disease metastasizes, this amount decreases further. The results of the study conducted by Kjaer show that plasma EGFR levels have predictive value for late-stage breast cancer and early-stage breast cancer.[50]

Conclusion. Biomarkers provide valuable insight into a breast cancer patient's prognosis and response to treatment. Serum biomarkers offer an attractive alternative to tissue biomarkers, especially in the setting of monitoring for disease recurrence or progression, following response to treatment, and even determining targetable mutations to direct therapy. CA15-3, CEA, and TPSA have low sensitivity in early breast cancer, but they are more practical in predicting disease prognosis, metastases, and recurrence. Cytokines (IL-6, TNF-alpha), VEGF, and EGFR are essential in disease pathogenesis and treatment processes and have been studied in many studies as predictive factors, they have proved useful adjuncts in the management of separate group in BC patient. For example, cytokines may be effective in the management of patients with metabolic syndrome or obese. Also, good results can be achieved using il-6 in managing infiltrative BC. Prospects can be reached by studying serum markers mentioned in people with diabetes, cardiovascular disease, and other comorbid conditions.

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