Review Article

Muc-1 Family Tumor Markers and Their Role in the Diagnosis of Breast Cancer, Review Article

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Abstract

Background & Objective: Tumor markers are elements produced by tumors or other cells in the body in response to cancer or some benign condition. Although most of these markers are made by normal cells as well as cancer cells, they are produced at much higher levels in cancerous conditions. This study aimed to provide a method for using tumor markers to diagnose cancer and detect the presence of metastasis and recurrence of the disease.

Materials & Methods: The present narrative review study was done by selecting the appropriate keywords and searching for research and review studies indexed in Google Scholar, PubMed, Science Direct, and SID databases.

Results: These studies often indicate the effective role of tumor markers in the MUC-1 family (especially Cancer antigen15-3 (CA15-3) and CEA (carcinoembryonic antigen) as the most widely used tumor markers in patients with breast cancer.

Conclusions: Based on information from studies on tumor markers, the combination of CEA, CA15-3, PRL (prolactin), KL-6 (Kerbs von den Lungen), Thioredoxin 1, and FER (ferritin) tumor markers can increase the sensitivity of early-stage breast cancer detection, and CA15-3 tumor markers can also be used to identify the presence or absence of metastasis to the axillary lymph nodes. The use of ultrasound (especially color Doppler) and its combination with CEA and CA15-3 tumor markers are recommended to improve the accuracy of a breast cancer diagnosis.

Keywords: CA15-3 protein, Carcinoembryonic Antigen, MUC1 protein

Introduction

Breast tissue is made up of three main parts: the lobules, ducts, and connective tissue. The lobules are the milk-producing glands, and the mammary ducts are the tubes that carry milk to the nipple; the connective tissue holds all parts of the breast together (1).

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Breast cancer is generally divided into two categories: non-invasive and invasive; cells that are limited to ducts and do not invade adipose and connective tissue are called non-invasive breast cancer, such as ductal carcinoma in situ (DCIS), which is very common and is seen in 90% of cases (1). Lobular carcinoma in situ (LCIS) is less common, and those cells that attack connective tissue and fat cause invasive breast cancer, which can lead to invasive lobular breast cancer (ILC), accounting for 10 to 15 percent of cases (1).

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Invasive ductal carcinoma (IDC), which accounts for 80 percent of cases is more common (1).

Breast cancer is the most common type of cancer in the world, accounting for 11.7% of all breast cancers of both sexes and at all ages. It is the most common cancer among women and is the leading cause of cancer death in women (2). The highest incidence and mortality rates from breast cancer are in Asia (2). Tumor markers which are produced by a tumor, are biomarkers found in blood, urine, or tissues of the body that can increase with one or more cancers. The ideal tumor marker should be specific and sensitive enough to detect small tumors and may be useful in early detection or screening assistance. They are more abundant in cancer tissue or the blood of cancer patients than in normal blood (3).

Many serum tumor markers have been described for the diagnosis and follow-up of breast cancer, including members of the MUC-1 family, for example, CA15-3, BR27.29 (breast cancer or cancer antigen 27.29), CA549 (cancer antigen 549), CEA, oncoproteins (e.g., HER-2 (Human epidermal growth factor receptor), and c-erbB-2 (receptor tyrosine-protein kinase erbB-2), cytokeratin's (e.g., tissue polypeptide antigen) as well as microRNAs (3).

The most common test for breast cancer diagnosis is mammography. The decision to perform a biopsy in women with suspicious mammographic findings should be made after mammography screening. BIRADS (Breast Imaging Reporting and Data System) classification is used for suspicious masses, which is an important and reliable method for assessing and estimating the risk of malignancy in breast lesions. In this system, the findings are classified 0 to 6, which are usually seen in BIRADS No. 4. With suspected abnormalities, a biopsy is decided, and an ultrasound is the first choice for breast cancer screening. This is the most widely used method of breast cancer screening, which is suitable for all age groups (4).

Materials and Methods

This narrative review study was performed by selecting appropriate keywords and searching for research and review studies indexed in Google Scholar, PubMed, Science Direct, and SID databases. A total of 35 articles (from 2000 to 2021) related to the subject were studied, extracted, summarized, and presented based on the information required.

Results

Tumor glycoprotein markers, cytokeratin's, and tumor marker tumors

A study carried out by Arslan et al. (5) using tumor markers CA15-3, CEA, and prolactin for early detection of breast cancer found that despite the 97.6% specificity of prolactin, it has the worst sensitivity to being diagnosed in the early stages of breast cancer. The combination of these three tumor markers can increase diagnostic sensitivity in the early stages of breast cancer but reduce specificity. Therefore, it cannot be used to screen or diagnose breast cancer, and the results also show that there is a greater correlation between the stage of the disease, the presence of axillary invasion, and metastasis for CA15-3 than for the two tumor markers CEA and PRL (prolactin) (Table 1) (5).

Table 1. Relationship between tumor markers and their levels in different stages of breast cancer (5)

Tumor marker	Stage 1	Stage 2	Stage 3	Stage 4
CA15-3	0%	22%	66.60%	62.50%
CEA	4.50%	22%	66.60%	50%
PRL	0%	6%	33.30%	0%

Another study by Yoshinari Ogawa et al. (2000) to evaluate serum KL-6 (Kerbs von den Lungen) (mucin-like glycoprotein) was used as a tumor marker in breast cancer. The results showed that the mean KL-6 titer of patients with primary breast cancer was 673 units per mL, which was significantly higher than benign and healthy individuals. And the KL-6 titer for patients with recurrent breast cancer was 1964 units per mL, which was higher than primary cancer. The susceptibility of KL-6 to primary cancer was 31%, recurrent cancer was 73%, and its specificity was 92%. In this study, it was also found that the sensitivity of KL-6 is higher than tumor markers CA15-3 and CEA and that the combination of these tumor markers with KL-6 increases the sensitivity for the diagnosis of primary breast cancer. As a result, it can be useful as a tumor marker for breast cancer, especially in monitoring the recurrence of the disease (6).

Another study by Kokko et al. (7) evaluated CA15-3 in the follow-up of localized breast cancer. Of the patients studied, only one-third were diagnosed with breast cancer recurrence by tumor markers, and it was concluded that tumor marker CA15-3 was not sufficiently sensitive to show the first recurrence earlier than other methods. Although it has good specificity, it seems that adding some markers such as CEA and ESR (erythrocyte sedimentation rate) can increase the sensitivity of this test (7). Sölétormos et al. (8) used tumor markers CA15-3, CEA, and TPA (Tissue polypeptide antigen) to monitor different stages of breast cancer. The following results were obtained: CA15-3 is a useful marker in the diagnosis of postoperative recurrence in patients with breast cancer. The combination of CEA and CA15-3 is also useful for evaluating patients after the first session of chemotherapy (8). In a study by Hashemi et al. (9), the role of tumor markers in breast cancer recurrence was investigated, and it was concluded that there was only a significant relationship between the CA15-3 tumor marker and recurrence. The important point of this study is that it may be possible to measure CA15-3 only once at the time of diagnosis, predict the possibility of recurrence in the patient, and, from the beginning, perform the treatment plan for these patients to reduce the possibility of recurrence at follow-up (9). In another study by Naghshvar et al. (10), the diagnostic value of blood levels of CA15-3 and CEA in breast tumors with axillary lymph node metastasis was examined, and the results showed that the levels of two tumor markers, CEA and CA15-3, showed a statistical difference between the two groups (patients with lymph node involvement and patients without lymph node metastasis). In general, the results of the study indicate that the CA15-3 tumor marker can be used to identify the presence or absence of axillary lymph node metastasis in breast malignancies, but the CEA is not very sensitive in this regard (10). A study by Laessig et al. (11) was performed on 119 patients with metastatic breast cancer and examined the importance of two tumor markers, CEA and CA15-3, in the progression of the disease in these patients. There is a clear correlation between CEA and CA15-3 in the progression of breast cancer, and as the disease progresses, the levels of these tumor markers increase. New metastases seen in patients or progressive disease (PD) were defined as the 1st PD, and subsequent metastasis or progression was considered the 2nd PD, etc. (Table 2) (11).

Table 2. The susceptibility of CEA and CA15-3 alone and in combination with each other and their relationship with disease progression (11)

Clinical course	Sensitivity (%)		
	CEA and CA15-3	CA15-3	CEA
Diagnosis of metastatic disease	53.5	71.8	80.3

st PD 1	52.9	69.4	80
st PD 2	61.6	80.2	83.7
st PD 3	70.8	87.5	94.4
st PD 4	79	88.7	85.2
st PD 5	80.9	87.2	95.7

The search for prognosticating and predictive molecular markers continues. One of these tumor markers, TIMP-1 (Tissue inhibitor of metalloproteinases 1), has been suggested as a prognostic marker and response to treatment in a study by Würtz et al. (12). Numerous studies have shown an association between TIMP-1 and the prognosis in breast cancer (12). Maric et al. (13) conducted a study and examined various tumor markers and concluded that: Tumor markers are usually less sensitive in the early stages of breast cancer, and screening with mammography or ultrasound and combining them with other tissue-based markers such as PR (Progesterone Receptor), ER (Estrogen receptor), and HER-2, and blood can be very helpful in diagnosing breast cancer (13).

According to the results of a study by Park et al. (14), thioredoxin in combination with CEA or CA15-3 was evaluated to improve sensitivity in the diagnosis of breast cancer. According to the results, thioredoxin is useful for the early detection of breast cancer and therefore its combination with CEA or CA15-3 can be very valuable for the diagnosis of breast cancer (14). Retrospective studies were performed by Petra Stieber et al. (2015) to evaluate the diagnostic effect of CA15-3 and CEA on the early detection of breast cancer metastases and reached a sensitivity of 46% for CEA alone and 55.6% for CA15-3 alone, a specificity of 98% for both, and a sensitivity of 66.3% for both tumor markers (15).

Zhao et al. (16) studied 111 patients with nipple discharge who had undergone breast surgery. They assessed its association with tumor markers CEA, CA15-3, CA199, CA724, and AFP (alpha-fetoprotein) and achieved these results: there was a statistically significant difference in nipple discharge in CEA and CA15-3 markers, but there was no difference in CA19, CA724, and AFP between the two groups. In summary, measurement of AFP, CA724, and CA199 tumor markers in nipple discharge have little clinical value, but CEA and CA15-3 can be used for early detection of breast cancer in high-risk populations (16).

In a study by Shao et al. (17), elevated levels of tumor markers CEA and CA15-3 were evaluated as prognostic parameters in different types of molecular subunits of breast cancer. The results showed an increase in the concentration of the axillary lymph nodes (TNM: Tumor Node Metastasis). Also, the prognostic significance of increased serum levels of CEA and CA15-3 was independently confirmed in luminal B breast cancer (17). In a study by Gioia et al. (18), several tumor markers were used for the early detection of tumor recurrence in patients with breast cancer. In a study of 47 patients with MBC (metastatic breast cancer), 26 had an increase in CEA and (or) CA15-3 by 55.3, which means these two tumor markers are directly related to the larger mass size and metastasis, and in the remaining 21 patients, there was no increase

in these tumor markers. Although CEA and CA15-3 alone are highly specific for the early detection of MBC, they have low sensitivity. However, when these two tumor markers were combined, the sensitivity increased to 87.2% and the specificity to 100%, and it was suggested that a combination of these two tumor markers could be used for early detection of MBC (18).

A study by Hepp et al. (19) showed CEA and CTC positivity before (CHT: chemotherapy) and 5 years after, which was significant but weak. Since no prognostic markers can reliably identify patients with recurrent breast cancer, further investigation is needed to assess the prognosis through these two independent tumor markers (19). A study by Fu et al. (20) examined the association between two marker tumors, CEA and CA153, and breast cancer. It was observed that malignant tumors show increased levels of CA15-3 at all stages, which is highly dependent on the stage of the tumor and increases as the tumor progresses (20). In a retrospective study by Wu et al. (21), in 1148 patients with breast cancer, two tumor markers, CEA and CA15-3, were measured preoperatively to predict axillary lymph node metastasis. The results showed that patients with increased tumor markers before surgery had an increased risk of developing ALNM (axillary lymph node metastasis). It seems that these two tumor markers can independently predict the incidence of ALNM in people with breast cancer (21).

In another study conducted by Svobodova et al. (22), the ability to predict cancer recurrence in patients 6 months after surgery was assessed by 47 tumor markers: CEA, TPS (tissue polypeptide specific antigen), and CA15-3 in 472 patients. The rate of TPS in the group of patients with tumor recurrence in the first month and 6 months after surgery was statistically significant compared to the group who did not have tumor recurrence. In addition, CEA and CA15-3 were also measured and did not show a statistically significant difference in any of the months studied. It was concluded that among these three tumor markers, TPS level at 6 months after surgery is the best indicator for predicting recurrence of breast cancer (22).

A study was conducted by Li et al. (23) to determine the prognostic value of preoperative CA15-3 and CEA in young (40≤) patients with breast cancer. In this study, it was found that CEA, and not CA15-3, predicts the prognosis of young patients with breast cancer (23). To monitor and follow up the recurrence of primary breast cancer in women who underwent a mastectomy and had no symptoms, a study by Nicolini et al. (24) combined measurement of three tumor markers, CEA, CA15-3, and TPS, using IRL (Individual reference limit). The results indicated sensitivity of 95.2%, specificity of 97.8%, and accuracy of 97.9% and finally concluded that combined measurement of CA 15-3, CEA, and TPA using the IRL to determine CC (Critical Changes) at the marker level is an accurate strategy for predicting postoperative outcome in asymptomatic breast cancer patients (24). In another study by Lian et al. (25), serum CEA, CA125, CA15-3, and FER (Ferritin) levels were measured, and the relationship between preoperative tumor markers and pathological findings was investigated. When evaluated in patients with breast cancer, it was observed that CA15-3, CEA, and FER were higher in patients with breast cancer than in the control group and those with benign tumors and it was also found that the level of each of the tumor markers CA15-3, CEA, and FER alone had low detection accuracy for the early stages of breast cancer due to their low sensitivity (25).

A study by Aksel et al. (26) evaluated the role of the AMDL-Dr 70 Elisa assay in breast cancer in patients undergoing breast biopsy and achieved the following results: DR 70 was 2.41 mg/mL in patients with breast cancer, 1.4 mg in patients with benign tumors and 1.2 mg/mL in controls (1.58 mg/mL cut off rate) and reached a sensitivity of 81% and a specificity of 79.3% for this test. It is briefly stated that when the DR-70 level is combined with mammography and breast ultrasound findings, decisions about breast biopsy can be made in women with radiologically

(BIRADS 4) breast lesions. DR 70 can be used to perform or not perform a biopsy in cases where there are differences in clinical and radiological findings (26). Another study by Hing et al. (27) on the clinical application of tumor markers CA15-3 and CEA aimed at the diagnostic accuracy of these two tumor markers in the monitoring of breast cancer and showed that these two tumor markers are complementary to each other in diagnosing the disease. While the sensitivity of CEA is about 75%, the specificity of CA 15-3 is about 97%, and the combination of the two increases the accuracy of the diagnosis (27). In another study by Gaughran et al. (28), patients with metastasis due to breast cancer were evaluated and the use of tumor markers CEA, CA125, CA15-3, and CA199 in MBC (metastatic breast cancer) was for CA125, CA15-3, CEA, and CA199, respectively. It was stated that CA15-3 and CA125 had a greater advantage in MBC than CEA alone. In a recent study, it was suggested that all 3 tumor markers (CEA, CA125, and CA15-3) be considered in patients with metastatic breast cancer (28). In a study by Lee et al. (29), they examined the extent of tumor markers CEA, CA15-3, and CA125 and the survival of breast cancer by their molecular subtypes. The results indicated that serum levels of CEA and CA15-3 before surgery varied between molecular subtypes of breast cancer and showed strong prognostic data in Chinese women with breast cancer. It was concluded that measuring CEA and CA15-3 before surgery can be useful in predicting breast cancer survival and treatment strategy of patients among luminal A subgroups (29). In a study, Monika Zajkowska et al. (30) compared the CA15-3 marker to VEGFR-3 (Vascular endothelial growth factor receptor) and concluded that VEGFR-3 had much higher diagnostic power than CA15-3 in the diagnosis of breast cancer (Table 3) (30).

Table 3. Plasma levels of the tumor markers CA15-3 and VEGFR-3 in breast cancer patients and controls, and the combination of these two tumor markers improves sensitivity (30)

Studied groups		VEGFR-3 (ng/mL)	CA15-3 (u/mL)
Breast cancer group Medium range	First Stage	86.47	16.7
	Second Stage	95.59	16.9
	Third Level	101.79	26.5
	The Fourth Step	132.42	45.1
	All Steps	98.03	19.95
control group Medium range	Benign Breast Mass	16.67	12.75
	Healthy Women	18.05	13.4
	All Steps	17.13	13.05

The role of MicroRna in the diagnosis of breast cancer

There have been many studies on MicroRna (MIR) and its association with breast cancer. In a study by Sun et al. (31), MIR155 was evaluated as a potential tumor marker for the follow-up of breast cancer patients, and it was observed that MIR155 levels were significantly increased in 55 cancer patients compared to 103 healthy individuals. The results showed that MIR155 levels decreased in 79% of patients after surgery and four courses of chemotherapy, but not in CEA, TPA, or CA15-3 (31). In another study by Gao et al. (32), the clinical significance of MIR21 compared with CA153 and CEA in breast cancer was evaluated. They observed that MIR21 levels in the breast cancer group were significantly increased compared to controls. The sensitivity and specificity of MIR21 were 87.6% and 87.3%, respectively, while the sensitivity for CEA and CA15-3 was 22.47 and 15.73%, respectively. It was briefly mentioned that MIR 21 refers to two tumor markers; it has a higher sensitivity in breast cancer patients and can be a diagnostic indicator for the early stages of the disease (32).

In a study by Zhao et al. (33), MIR 195 was evaluated as a potential tumor marker in the diagnosis of breast cancer. The results of this study showed MIR 195 is more sensitive to CEA and CA15-3 than ever before, especially for the early detection of cancer (33). In a study by Wei et al. (34), it was identified that MIR223 is a potential tumor marker in breast cancer. FXO1 (Forkhead box protein O1) is the putative target of MIR223 that regulates it. The results indicate that MIR223 expression is higher in patients with breast cancer than in healthy individuals. MIR223 expression increases the expression of FOXO1 protein in breast cancer cells in MCF-7 (Michigan Cancer Foundation-7). Meanwhile, MCF-7 breast cancer cells are suppressed after FOXO1 regulation. As a result, it was shown that MIR223 can, by targeting FOXO 1, inhibit the cell proliferation of cancer cells (34). In another study by Zaleski et al. (35), MIR34a was used to improve sensitivity in the diagnosis of breast cancer along with the widely used tumor markers CEA and CA15-3. It was observed that the use of MIR34a provides valuable information for tumor diagnosis and staging. Of all the mirs, only MIR34a can distinguish between breast cancer and benign masses, and so it turned out that MIR34a level correlates with tumor stage and tumor receptor status (35).

Color Doppler ultrasound and tumor markers in the detection and monitoring of breast cancer

In a study by Song et al. (36), the clinical value of color Doppler ultrasound in combination with tumor markers CEA, CA15-3, and TSGF (tumor-specific growth factor) in the follow-up of breast cancer was evaluated. The results indicated that the expression level of the three tumor markers mentioned in the breast cancer group was significantly higher than the benign lesion group. In the breast cancer group, level 3 markers were significantly higher in patients with advanced and recurrent stages compared to patients with early-stage and non-recurrent cancer; Color Doppler ultrasound's sensitivity, accuracy, and negative prognosis, when combined with TSGF, CEA, and CA15-3 tumor markers, are 90.20%, 95.15%, and 88.89%, respectively, which is significantly higher than any of these methods alone. This study showed that the sensitivity and accuracy of color Doppler ultrasound in diagnosing breast cancer are 77.67% and 79.74%, respectively, which is higher than any of these methods (Table 4). Therefore, the use of color Doppler ultrasound with 3 tumor markers can be mentioned as an effective and useful tool to improve the accuracy of breast cancer diagnosis (36).

Table 4. Comparison of the clinical value of color Doppler ultrasound, CEA, CA15-3, and TSGF alone and in combination with each other in breast cancer detection (36)

Diagnosis	Sensitivity	significantly	Accuracy	PPV	NPV
ultrasound	77.67	84	79.74	90.91	64.62
CA15-3	64.08	92	73.2	92.49	55.42
CEA	62.14	90	71.24	92.75	53.57
TSGF	66.02	90	73.86	93.15	56.25
Combine all factors	95.15	80	90.2	90.74	88.89
P-value	0.001	0.341	0.001	0.771	0.001

Discussion

To achieve a successful diagnosis and treatment of breast cancer, finding indicators for early detection and follow-up of patients' treatment are crucial. In most studies, the combination of tumor markers CEA, CA15-3, PRL, KL-6, Thioredoxin 1, and FER leads to increased sensitivity in the early detection of breast cancer. Also, their combination is very useful for monitoring the recurrence of the disease (5, 6, 15, 16, 18, 25). CA15-3 can be useful as a marker to be used to identify the presence or absence of axillary lymph node metastasis and, given the very close correlation between this tumor marker and the progression of malignancy, by measuring the level of CA15-3, the possibility of recurrence can be predicted and started from the very beginning of the patients' treatment program to reduce the likelihood of recurrence at follow-up (5, 8-10, 17, 21). The simultaneous assessment of CEA and CA15-3 tumor markers are very useful in the early detection of breast cancer and prediction of metastasis due to its specificity and high sensitivity (15-18, 28). To map out an accurate strategy to predict postoperative outcomes in patients undergoing mastectomy and those who are asymptomatic, the combination of three tumor markers (CEA, CA15-3, and TPS) is used to monitor and follow the recurrence of breast cancer (30). The use of MIR155, MIR-21, MIR195, and MIR34a along with CEA, CA15-3, and TPA markers is very effective in early breast cancer diagnosis due to the higher sensitivity of MIRs. It is also recommended to use them to check the response to cancer treatment (31-33, 35). Of all the MIRs, only MIR34a can differentiate between breast cancer and benign masses (35). Due to the very high capability of ultrasound (especially color Doppler) in distinguishing between benign and malignant masses and the appearance of tumor angiogenesis, the use of this method and its combination with

CEA and CA15-3 tumor markers is recommended to improve the accuracy of breast cancer diagnosis (36).

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Conflict of interests

The authors declare that they have no conflict of interest.

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