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Tumor markers of breast cancer: New prospectives

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ABSTRACT

Tumor markers are substances produced by the tumors or by other cells of the body in response to cancer or certain benign conditions. Although most of these markers are made by the normal cells as well as by cancer cells, they are produced at much higher levels in cancerous conditions. These markers are used to evaluate the patient's response to treatment and to detect the presence of metastasis or recurrence. Breast cancer is one of the most common malignancies in females worldwide. The CA 27-29, CA 15-3, CA27.29, carcinoembryonic antigen, tissue polypeptide specific antigen, p53, cathepsin D, cyclin E, nestin and HER-2 are tumor markers that are often expressed in people with breast cancer. They play a crucial role in diagnosis, monitoring response to therapy, early detection of metastasis and determination of recurrence in patients with breast cancer.

1. Introduction

A tumor marker is a biomarker that is found in blood, urine or body tissues that can be elevated by the presence of one or more types of cancer. It is produced either by the tumor itself or by the host in the response to a tumor.[1] The ideal tumor marker should be both specific and sensitive to detect small tumors to allow early diagnosis or help in screening. Few markers are specific for a single tumor. Most markers are produced by different tumors of the same tissue type. They are present in higher quantities in cancer tissue or in blood from cancer patients more than in the blood of normal subjects. Tumor markers are mostly useful in evaluating the progression of the disease status after initial chemotherapy and radiotherapy to monitor subsequent treatment strategies.[2]

Breast cancer is the second most common type of cancer after lung cancer (10.4% of all cancer incidence, both sexes counted) and the fifth most common cause of cancer death.[3] It is a disease caused by a combination of genetic and environmental factors. Numerous risk factors that may be associated with breast cancer have been recognized. Not all breast cancer patients have the same clinical picture. Some factors increase a woman's risk of breast cancer more than others.[4]

Early detection of breast cancer both primary and recurrent, is of considerable clinical importance, and it can be used to make treatment decisions while tumor burden is low, and when patients are most likely to respond to adjuvant therapy.[5] In recent decades, the serum concentration of tumor markers has been used to detect tumor activity. Tumor markers provide a minimally invasive cost-effective source of data valuable for monitoring disease course, determining prognosis, and helping in treatment planning. An understanding of the individual test characteristics and limitations is important for optimal use and accurate interpretation of results.[6] The real usefulness of tumor markers in the management of breast cancer has been questioned because of the low diagnostic sensitivity for early disease.[7]

The American Society of Clinical Oncology (ASCO) has updated its recommendations for use of tumor markers in prevention, screening, treatment and surveillance of breast cancer. 13 categories of breast tumor markers were considered. The tumor markers that showed evidence of clinical utility and were recommended for use in practice include CA 15-3, CA 27.29, Carcinoembryonic antigen (CEA), Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2 (HER2), Urokinase plasminogen activator (uPA), Plasminogen activator inhibitor 1 (PAI-1) and multiparameter assays for gene expression.[8] However, other categories are also used in screening of breast cancer but they demonstrated insufficient evidence support routine use in clinical practice including P53, cathepsin D, cyclin E and nestin.[7]

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2. Carcinoembrvonic antigen (CEA)

Carcinoembryonic antigen (CEA), which belongs to a family of related cell surface glycoproteins, is the most widely used tumor marker in the clinical practice. It is a tumor marker for colorectal, gastrointestinal, lung and breast cancer.[9] CEA was first identified as a tumor specific antigen found in extracts of tumor tissue. It is also found in normal foetal gastrointestinal tract epithelial cells. It is a glycoprotein that contains 45−50% carbohydrates. It is a single polypeptide chain consisting of 641 aminoacids, with lysine at its N-terminal position.[10]

The human carcinoembryonic antigen (CEA) family is composed of 29 genes arranged on chromosome 19ql3.2, of which 18 are expressed. These genes are classified into two major subfamilies, the CEA cellular adhesion molecule (CEACAM) and the pregnancy-specific glycoprotein subgroups.[11] The CEACAM family belongs to the immunoglobulin superfamily. The CEACAM proteins can interact homophilically (CEA binding to CEA) and heterophilically (CEA binding to non CEA molecules) with each other, suggesting that CEA might act as an adhesion molecule. Because alternations in cell adhesions are involved in cancer invasion and metastasis, it was further suggested that CEA may play a crucial role in these processes.[12]

Continuous rising level of CEA in breast cancer may explain either cancer not responding to treatment, or recurrence after treatment. As steadily rising CEA may be the first sign of cancer recurrence after treatment, the lead time from CEA elevation to clinical recurrence is about 5 months.[13] Also, patients with advanced cancer or metastatic cancer may have higher CEA levels rather than in patients with localized diseases.[9] Because CEA lacks disease sensitivity and specificity, it cannot be used for screening the general asymptomatic population, a subpopulation with a high risk for malignancies, or for independently diagnosing cancer. However, CEA can be used to help diagnosis, clinical staging, to detect recurrence in patients who have undergone surgery, and to monitor the therapeutic response in patients undergoing chemotherapy or radiotherapy.[14]

In breast cancer, elevated CEA is associated with metastatic disease. Preoperative CEA measurements have been shown to correlate with pathological stage and tumor extent and is stage dependent. Circulating levels of CEA in breast cancer patients are directly dependable on the size of both primary and metastatic tumor. For breast cancer, CEA is being replaced by other more specific markers, such as CA 15-3.[15] Sławicki et al.[16] reported that CEA alone is non specific for diagnosis of breast cancer. Geng et al.[17] suggested that there should be an association between CEA, CA 15-3 and the clinicopathological parameters for proper diagnosis in patients with metastatic breast cancer.

3. Cancer antigen (CA) 15-3

The name of this marker is derived from a combination of the molecular structure and the assays developed for its detection. The numbers 15-3 refer to the antibodies used in immunoassays for these antigens.[9] CA 15-3 is a carbohydrate-containing protein antigen called mucin (MUC). Mucins are large transmembrane glycoproteins with extracellular domains formed of a highly O-linked glycosylated protein core consisting of a variable number of highly conserved 20-amino acid repeat units, classified into 7 families, MUC1 to MUC7, according to their genetic and biomolecular characteristics.[18] CA 15-3 belongs to the MUC1 family. Although the MUC1 gene is found in several tissues, it produces an apparently identical core protein. The variation in the extent of glycosylation (carbohydrate content) is the distinguishing feature between different tissue sources. In breast tissue, the carbohydrate content is approximately 50%. The exact physiological functions of MUC1 proteins are not completely known, but it appears to reduce cell-to-cell interaction and may also inhibit tumor cell lysis.[19]

The MUC1 gene is overexpressed in malignant breast tumors, allowing use of gene product CA 15-3 as tumor marker for breast cancer.[18] CA 15-3 concentrations in blood can be used for screening, not only for breast cancer but also for other malignancies, includi pancreatic, lung, ovarian, colon and liver cancer. However, it was also reported to be elevated in benign liver and benign breast diseases (False positive results).[20] It is more useful in determining the prognosis of breast cancer and to monitor the efficacy of therapy as it was shown that the serum concentration and the proportion of patients with elevated values of this marker tend to increase with the severity (stage) of the disease and/or size of the tumor.[9] Lumachi et al.[21] suggested that CEA and CA 15-3 should be considered complementary in detecting recurrence of breast cancer but their sensitivity is low and independent of the majority of the prognostic parameters that may be considered before relapse. Darlix et al.[22] reported that serum CA 15-3 level is independent prognostic factor in metastatic breast cancer patients.

4. CA 27.29

CA27.29 is a carbohydrate-containing protein antigen that serves as a tumor marker for breast cancer. It is also called breast carcinoma-associated antigen.[23] It is produced by the MUC-1 gene. CA 27.29 is highly associated with breast cancer, as 80% of women with breast cancer have an increased CA 27-29 levels. However, CA 27.29 can also be found in patients with other malignancies or with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts. Therefore, elevation of this marker is not organ specific.[24]

CA 27.29 has clinical performance similar to that of CA 15.3 in patients with breast cancer. Evidence showed that CA 27.29 may be a more sensitive but less specific marker than CA 15-3, but this has not bee definitively demonstrated and it is generally felt that they are essentially equivalent for most clinical purposes.[25] The low sensitivity and lack of specificity preclude the use of this assay for screening for breast cancer. It appears to be more useful in detecting the disease progression and metastatic involvement. CA27.29 appears to be more sensitive and specific than CEA, but it performs similarly as compared to CA 153 for earlier detection of metastatic disease during follow-up screening.[26] Gion et al.[27] reported that CA27.29 provides comparable results to CA15.3. They found that CA27.29 seems to be more sensitive than CA15.3 to limited variations of tumor extension. However, it cannot help clinicians in distinguishing stage I patients from stage II patients. Rack et al.[28] indicated that there is a close relationship between CA27.29 levels and tumor mass. They attributed the increased values after completion of chemotherapy to treatment effects and suggested that these values should be considered with caution.

5. Estrogen receptor (ER)

ER is one of the successful tumor markers in breast cancer. The ER has a role in cellular growth, proliferation and differentiation.[29] In addition to prognostic value, ER is the most important biologic marker of response to treatment in breast cancer. It is a member of the family of nuclear steroid receptors and functions as a transcriptional regulator, which is controlled by the hormone 17p-estradiol estrogen (E2).[30] Hormone activated estrogen receptors form dimers, and since the two are coexpressed in many cell types, the receptors may form ERa homodimers or ERp heterodimers. ERa is localized on human chromosome 6, in contrast to ERp, which i chromosome 14.[31]

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