

Serum Tumor Markers in Breast Cancer: Are They of Clinical Value?

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Background: Although multiple serum-based tumor markers have been described for breast cancer, such as CA 15-3, BR 27.29 (CA27.29), carcinoembryonic antigen (CEA), tissue polypeptide antigen, tissue polypeptide specific antigen, and HER-2 (the extracellular domain), the most widely used are CA 15-3 and CEA.

Methods: The literature relevant to serum tumor markers in breast cancer was reviewed. Particular attention was given to systematic reviews, prospective randomized trials, and guidelines issued by expert panels.

Results: Because of a lack of sensitivity for early disease and lack of specificity, none of the available markers is of value for the detection of early breast cancer. High preoperative concentrations of CA 15-3 are, however, associated with adverse patient outcome. Although serial determinations of tumor markers after primary treatment for breast cancer can preclinically detect recurrent/metastatic disease with lead times of ~2–9 months, the clinical value of this lead time remains to be determined. Serum markers, however, are the only validated approach for monitoring treatment in patients with advanced disease that cannot be evaluated by use of conventional criteria.

Conclusions: CA 15-3 is one of the first circulating prognostic factors for breast cancer. Preoperative concentrations thus might be combined with existing prognostic factors for predicting outcome in patients with newly diagnosed breast cancer. At present, the most important clinical application of CA 15-3 is in monitoring therapy in patients with advanced breast cancer that is not assessable by existing clinical or radiologic procedures.

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For many malignancies, serum tumor markers play an important role in patient management (1–5) (Table 1). In breast cancer, however, the role of serum markers is less well established. The most widely used serum markers in breast cancer are CA 15-3 and carcinoembryonic antigen (CEA).¹ Less widely used markers include BR 27.29 (also known as CA27.29), tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS) and the shed form of HER-2 [Table 2; for a review, see Refs. (6–8)]. The potential uses of serum markers in breast cancer include aiding early diagnosis, determining prognosis, prospectively predicting response or resistance to specific therapies, surveillance after primary surgery, and monitoring therapy in patients with advanced disease. The aim of this review is to examine the role of serum tumor markers in the detection and management of patients with breast cancer. As CA 15-3 is the most widely used serum marker in breast cancer, most of the review will focus on it.

Aiding Early Diagnosis

Lack of sensitivity for early-stage disease combined with a lack of specificity precludes the use of all existing serum markers for the early diagnosis of breast cancer. For example, CA 15-3 concentrations are increased in ~10% of patients with stage I disease, 20% with stage II disease, 40% with stage III disease, and 75% with stage IV disease (9). According to an American Society of Clinical Oncology (ASCO) Expert Panel, a CA 15-3 concentration 5- to 10-fold above the upper limit of the reference interval could alert a physician to the presence of metastatic disease (9). However, a low concentration does not exclude metastasis (9).

As well as lacking sensitivity for early disease, CA 15-3 also lacks specificity for breast cancer. Increased concentrations of the marker can be found in a small proportion of apparently healthy individuals (~5%); in patients with

¹ Nonstandard abbreviations: CEA, carcinoembryonic antigen; TPA, tissue polypeptide antigen; TPS, tissue polypeptide-specific antigen; ASCO, American Society of Clinical Oncology; EGTm, European Group on Tumor Markers; and UICC, International Union against Cancer.

Table 1. Malignancies in which serum tumor markers play an important role in patient management.

Malignancy	Marker(s)	Use of marker(s)	Reference
Nonseminomatous germ cell cancer	AFP; ^a HCG	Prognosis, surveillance, and monitoring of therapy	(1)
Trophoblastic disease	HCG	Surveillance and monitoring of treatment	(2)
Ovarian cancer	CA 125	Monitoring of therapy	(3)
Colorectal cancer	CEA	Surveillance and monitoring of therapy	(4)
Prostate cancer	PSA	Prognosis, surveillance, and monitoring of therapy	(5)

^a AFP, α -fetoprotein; HCG, human chorionic gonadotropin; PSA, prostate-specific antigen.

certain benign diseases, especially liver disease; and in patients with other types of advanced adenocarcinomas (6–9). Consequently, for the foreseeable future, mammography and histopathology will remain the primary modalities for detecting early breast cancer.

Determining Prognosis

Available prognostic factors for breast cancer include pathology criteria such as tumor size, tumor grade, and lymph node status (10), as well as newer biological factors such as hormone receptors, HER-2, urokinase plasminogen activator, and plasminogen activator inhibitor 1 (11, 12). All of these factors require tumor tissue, thus necessitating either biopsy or surgery. Clearly, it would be desirable to have a circulating prognostic marker for breast cancer, particularly if it provided independent prognostic information.

At least 10 published studies involving >4000 patients have addressed the relationship between preoperative concentrations of CA 15-3 and patient outcome (Table 3) (13–23). Although a range of cutoff points were used (25–40 kilounits/L), all of the identified studies apart from one concluded that high concentrations of the marker at initial presentation predicted adverse patient outcome. Indeed, in some studies, the prognostic impact of CA 15-3 was independent of tumor size and axillary nodal status (15, 22, 23). Significantly, in 2 reports (22, 23), CA 15-3 was found to be prognostic in lymph node-negative breast cancer patients, the subgroup in which new prognostic factors are most urgently required. In another study, however, CA 15-3 was not prognostic in patients free of axillary nodal metastases (24). A pooled analysis of all data relating preoperative concentrations of CA 15-3 with patient outcome should now be carried out.

Although most studies relating CA 15-3 to prognosis have used preoperative values, concentrations during

follow-up can also provide prognostic information. Thus, Tampellini et al. (25) reported that patients with CA 15-3 values <30 kilounits/L at the time of first recurrence survived significantly longer than those with higher concentrations. In another report, De La Lande et al. (26) found that patients with a CA 15-3 lead time >30 days had a better prognosis than those with a shorter lead time. In that study (26), both the time interval between diagnosis and first abnormal CA 15-3 concentration (cutoff, 47 kilounits/L) were also of prognostic value.

These findings suggest that determination of CA 15-3 can provide real-time prognostic information in patients with breast cancer. Indeed, preoperative concentrations could be combined with existing prognostic factors for selecting patients for adjuvant therapy. For example, in lymph node-negative patients, preoperative concentrations of CA 15-3 might be combined with tumor size, tumor grade, estrogen receptor status, and HER-2 status for selecting who should or should not receive adjuvant chemotherapy.

Serum concentrations of the shed form of HER-2 have also been widely investigated for potential prognostic value in breast cancer. After performing a systematic review of the literature, Carney et al. (27) identified 20

Table 3. Published studies describing a prognostic value for preoperative concentrations of CA 15-3 in breast cancer.

No. of patients	Cutoff, kilounits/L	DFI ^a	OS	Multivariate analysis	Follow-up, years	Reference
97	20	Yes	ND	ND	NS	(13)
60	30	Yes	ND	ND	1–2	(14)
368	30	ND	Yes	Yes	3.3 (median)	(15)
186	35	NS	ND		0–8	(16)
673	30	Yes	Yes	ND	0–7	(17)
414	30	Yes	Yes	ND	NS	(18)
364	40	Yes	Yes	ND	6 (median)	(19)
362	31	Yes	ND		5.8 (median)	(20) ^b
1046	25	Yes	Yes	No ^c	1.8–12.7	(21)
272	30	Yes	ND	Yes	9.8 (median)	(22)
600	30	ND	Yes	Yes	6.3 (median)	(23) ^d
1057	30	Yes	Yes	No	8 (mean)	(24) ^e

^a DFI, disease-free interval; OS, overall survival; ND, not done; NS, not stated.

^b This study used only node-negative patients.

^c Not prognostic with CEA included in multivariate analysis.

^d Update with increased numbers of a previous study (15).

^e Follow-up period was for patients free of relapse at time of analysis.

Table 2. List of most widely used serum tumor markers in breast cancer.

Marker	Protein(s) detected
CA 15-3	MUC-1
BR 27.29 (CA27.29)	MUC-1
CEA	CEA
TPA	Fragments of cytokeratin 8, 18, and 19
TPS	Fragments of cytokeratin 18
HER-2 (shed form)	Extracellular form of HER-2

publications involving >4000 patients that related serum HER-2 concentration to outcome. These studies showed that high HER-2 concentrations in patients with either early or metastatic breast cancer predicted adverse outcome as demonstrated by decreased time to disease progression, decreased disease-free survival, and decreased overall survival. It was not clear, however, whether the prognostic information provided by HER-2 was independent of the traditional factors.

Although less widely investigated as a prognostic factor than either CA 15-3 or HER-2, high preoperative concentrations of CEA are also associated with poor prognosis in breast cancer (16, 19, 21, 24). Furthermore, in one large study ($n = 1046$), patients with a decrease of >33% between pre- and postoperative concentrations were found to have a worse outcome than those with a lesser decrease (21). In multivariate analysis, this decrease in CEA predicted outcome independent of tumor size, lymph node status, and progesterone receptors.

Predicting Response to Therapy

As with prognostic factors, the available therapy-predictive markers in breast cancer, such as estrogen receptor, progesterone receptor, and HER-2 (28), all require tumor tissue for analysis. Preliminary findings, however, suggest that high serum HER-2 concentrations are associated with both poor response to endocrine therapy and cyclophosphamide-methotrexate-5-fluorouracil-based chemotherapy but can predict an improved response to a combination of trastuzumab (Herceptin) and chemotherapy [for a review, see Ref. (27)]. These preliminary findings should now be confirmed in a large prospective trial.

CA 15-3 and other MUC-1-related markers may also have a role in predicting response to therapy. Ren et al. (29) recently reported that overexpression of MUC-1 (the antigen detected in CA 15-3 and BR 27.29 assays) in a mouse model system conferred resistance to cis-platinum. This resistance appeared to result from the ability of MUC-1 to inhibit apoptosis. Clearly, studies should now be carried out to determine whether either tumor tissue or serum concentrations of MUC-1-related markers predict response/resistance in patients undergoing treatment with platinum-based therapies.

Surveillance after Primary Treatment

Follow-up of patients after primary treatment for breast cancer with clinical examination, radiology, and biochemical testing is now standard practice in many centers. This practice is based on the assumption that the early detection of recurrent or metastatic disease enhances the chances of cure or survival. The evidence currently available, however, does not support this widely held assumption.

Two large multicenter randomized prospective trials (each with >1000 patients) compared outcome in patients followed up with clinical visits and mammography vs

those who were followed up with an intensive regime that included radiology and traditional laboratory testing (30, 31). Both studies concluded that use of an intensive follow-up program failed to improve outcome. Similarly, after pooling of the data from the above 2 studies, no significant difference in either disease-free interval or overall survival emerged between patients with intensive vs nonintensive surveillance (32).

In addition to these 2 large prospective trials, a systematic review of studies comparing control vs intensive follow-up regimes for newly diagnosed breast cancer patients has also been carried out (33). Of 4418 reports identified, 38 were considered eligible for analysis. Although the data were not sufficiently homogeneous to integrate statistically, the authors concluded that patient survival and quality of life were not affected by the intensity of follow-up or location of care. The authors also concluded that there was insufficient evidence to draw broad conclusions with respect to best practice for breast cancer follow-up care regarding morbidity reduction, cost-effectiveness, and patient involvement in care.

Clearly, the available data do not support the use of an intensive follow-up program using standard biochemical testing and radiology after primary treatment for breast cancer. However, as pointed out by Emens and Davidson (34), the value of surveillance depends on both the sensitivity and specificity of the available diagnostic tests as well as the efficacy of therapy available for recurrent/metastatic disease.

Diagnostic tests and treatments are continually evolving. Several of the published studies comparing minimal vs intensive follow-up may therefore have limitations with respect to the modern management of patients with breast cancer. These limitations include the following:

- Use of older and less sensitive biochemical tests rather than the newer tumor markers such as CA 15-3. For example, in a large randomized trial that enrolled 4105 patients, routine biochemical tests such as alkaline phosphatase, aspartate transaminase, γ -glutamyltransferase, bilirubin, calcium, and creatinine were shown to be of limited value in detecting metastasis after treatment for operable breast cancer (35).
- Use of older radiologic procedures rather than newer procedures such as computed tomography, magnetic resonance imaging, and positron emission tomography scanning.
- Most of the reports comparing outcome in control and intensively followed-up patients predate the availability of new treatments for recurrent/metastatic breast cancer, such as the taxanes, the new generation of aromatase inhibitors, and trastuzumab (36).

In recent years, several reports have shown that serial concentrations of tumor markers increase before radiologic or clinical evidence of disease relapse [for reviews, see Refs. (6–9)]. In a review of the literature, an ASCO Expert Panel identified 12 studies that used serial CA 15-3

measurements to monitor patients for recurrence after breast cancer surgery. In 7 of these trials, data were available in sufficient detail to allow pooling of results. Summation of the data showed that 67% of 352 patients had increased CA 15-3 either before or at the time of recurrence (9). In 1320 patients without evidence of recurrence at the time of study, 92% had CA 15-3 concentrations within reference values. The mean lead time from marker increase to clinical diagnosis of recurrence varied from 2 to 9 months.

Although serial CA 15-3 concentrations can preclinically detect recurrent/metastatic disease, it is unclear whether the introduction of early treatment based on this lead time improves disease-free survival, overall survival, or quality of life for patients. In an attempt to address these issues, several small-scale studies have been carried out. In one of the first of these, Jager (37) randomized patients with increasing concentrations of tumor markers (CA 15-3 or CEA) but without evidence of metastatic disease to receive ($n = 21$) or not receive ($n = 26$) medroxyprogesterone acetate. For the untreated patients, the median time interval between increase in marker concentration and detectable metastasis was 4 months, but for the treated patients it was >36 months.

In a second study, Nicolini and coworkers (38, 39) compared outcome in 36 asymptomatic patients who received salvage treatment based on tumor marker increases (CA 15-3, CEA, or TPA) vs 32 patients who were given treatment only after radiologic confirmation of metastasis. Survival from both the time of mastectomy and salvage treatment was significantly improved in the group with tumor marker-guided treatment than in those treated conservatively.

In a third study, Kovner et al. (40) randomized asymptomatic patients with increasing mammary cancer antigen concentrations to receive ($n = 23$) or not receive tamoxifen ($n = 26$). After a median follow-up of 11 months, 7 of 29 (24%) in the control group had relapsed, whereas none of the 23 patients randomized to receive treatment developed a recurrence ($P = 0.012$).

Although these 3 studies contained small numbers of patients, they all suggested that early treatment based exclusively on increasing marker concentrations improved prognosis. These findings, however, are not sufficiently strong to recommend a change in clinical practice, i.e., to recommend that asymptomatic patients with increasing marker concentrations should start new therapy. Many expert panels (including ASCO, European Society of Medical Oncology, and European Society of Mastology) therefore recommend that tumor markers should not be used in the routine surveillance of patients after primary treatment for breast cancer (9, 41–43). Other organizations, such as the European Group on Tumor Markers (EGTM) as well as the National Academy of Clinical Biochemistry (NACB), however, recommend the use of tumor markers during surveillance (44, 45).

Monitoring Response to Therapy in Advanced Disease

Traditionally, International Union against Cancer (UICC) criteria have been used for assessing response to therapy in patients with advanced breast cancer (41). UICC criteria include physical examination, measurement of lesions, radiology, and isotope scanning (46). Multiple studies (47–49) and 3 multicenter trials (50–52), however, have shown that changes in serial concentrations of tumor markers, particularly CA 15-3, correlate with response. In 2 of these multicenter trials, the alterations in tumor marker concentrations were shown to correlate well with UICC criteria (50, 51). Indeed, the use of markers to monitor therapy has several advantages over conventional criteria, including increased sensitivity, more objective measurement, and more convenience for patients (6, 7).

On the basis of data from 11 low-level evidence studies (9), an ASCO Panel concluded that 66% of patients with chemotherapy-induced disease regression exhibited decreases in marker concentrations, 73% of those with stable disease had no significant change in marker concentrations, and 80% with progressive disease displayed increasing concentrations (9). In most of these studies, a change in CA 15-3 concentration $>25\%$ was regarded as a significant alteration.

The same ASCO Panel also reviewed the literature on the use of CEA in monitoring response to treatment (9). Eighteen low-level evidence studies were reviewed. Of these, 6 reported results only in patients with high concentrations of CEA. Overall, 82% of the patients were found to have decreasing concentrations with disease response, whereas 74% had increasing concentrations with progressive disease. Of the 12 studies reporting results for patients with advanced disease irrespective of whether CEA was increased, 61% of patients showed a decrease in CEA concentrations with tumor response and 65% showed an increase with tumor progression.

Although the available data show relatively good correlations between alterations in serial tumor marker concentrations and response to therapy in advanced breast cancer, the ASCO Panel concluded that neither CA 15-3 nor CEA should be routinely used for this purpose (9, 41). However, the guidelines also stated “that in exceptional circumstances such as the presence of osseous metastasis, which are difficult to evaluate clinically, the marker level may be able to support the clinical estimate of disease status. However, the marker cannot in any situation stand alone to define response to treatment” (41). The ASCO Panel did not address the use of breast cancer serum markers other than CA 15-3 and CEA.

Although the ASCO Panel was unable to recommend routine use of tumor markers for monitoring treatment in advanced breast cancer, according to Cheung et al. (7), measurement of tumor markers is the only validated method for determining response in patients with disease not assessable by UICC criteria. Overall, 10%–40% of patients with breast cancer have nonassessable disease,

i.e., those with irradiated lesions, pleural effusion, ascites, lytic bone disease, and sclerotic bone disease (7).

In contrast to the ASCO Panel, both the NACB and EGTM Panels recommended use of CA 15-3 for monitoring therapy in patients with advanced breast cancer (44, 45). According to the EGTM Panel, markers should be measured before every chemotherapy course and at 3-month intervals for patients receiving hormone therapy (44). This Panel defined a clinically significant increase in marker concentration as an increase of at least 25% over the previous value. This increased concentration should be confirmed with a second sample taken within 1 month. The Panel also stated that a confirmed decrease in marker concentration of >50% was consistent with tumor regression (44).

Although CA 15-3 and CEA are the most widely used markers in monitoring chemotherapy in patients with advanced breast cancer, emerging data suggest that serum HER-2 may be of use in patients undergoing treatment with trastuzumab-based therapy. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER-2 and is now widely used in combination with chemotherapy for the treatment of patients with HER-2-overexpressing advanced breast cancer (53).

In a recent retrospective study, Eesteva et al. (54) compared serum HER-2 and CA 15-3 for monitoring trastuzumab-based therapy in 99 patients with advanced breast cancer. Concordance between clinical status and HER-2 concentrations was 0.793 compared with 0.627 for CA 15-3. When both markers were combined, the concordance with clinical status increased to 0.83. Although progression-free survival did not differ significantly between patients with increased vs normal baseline HER-2 concentrations, it did differ according to whether the patient's HER-2 concentration at 2 to 4 weeks after start of therapy was >77% or <77% of the baseline value. For patients with HER-2 concentrations >77% of baseline, the median progression-free survival was 217 days, whereas for those with concentrations <77% of baseline it was 587 days ($P = 0.043$).

In another preliminary report, Kostler et al. (55) showed that in patients responding to trastuzumab-based therapy, serum HER-2 concentrations decreased significantly as early as from day 8 of treatment. In contrast, no significant changes were observed in patients with progressive disease. Using multiple logistic regression analysis, they found that change in HER-2 concentrations were the only factor that predicted the likelihood of response after 8 days of treatment. Furthermore, measurement of serial concentrations of HER-2 predicted risk of disease progression as early as day 15 of treatment.

These preliminary findings suggest that serum HER-2 may be an early indicator of response and progression-free survival in patients with advanced breast cancer undergoing trastuzumab-based treatment. These early findings, however, require validation in a large prospec-

tive trial before serum HER-2 can be recommended for monitoring of trastuzumab-based treatment in patients with advanced breast cancer.

Caveats in the Use of Tumor Markers for Surveillance and Monitoring of Therapy in Patients with Breast Cancer

Despite recommendations from the ASCO Panel (9, 41), serum tumor markers such as CA 15-3 are widely used, particularly in Europe, for both postoperative surveillance and monitoring therapy in patients with advanced breast cancer. When serum tumor markers are used in these settings, several points should be borne in mind, including the following:

- None of the available markers is increased in all patients with breast cancer even in the presence of advanced disease. For those patients with advanced disease who do not have increased CA 15-3 concentrations, other markers, such as CEA, TPA, TPS, or the shed form of HER-2, may be considered for monitoring purposes.
- The available markers are most sensitive for detecting distant metastases and are of little value in diagnosing locoregional recurrences (56–59).
- The magnitude of change between successive marker concentrations that constitutes a critical change is not clear. According to Soletormos et al. (60), this so-called critical difference should be based on both the analytical imprecision of the assay (CV_a) and the normal intraindividual biological variation (CV_I). Assuming CV_a values of 11.2% for CA 15-3, 9.5% for CEA, and 11% for TPA, successive concentrations must differ by 30%, 31%, and 72%, respectively, for P values to be significant at a 0.05 level (60).
- Paradoxical patterns of tumor marker concentrations after initiation of chemotherapy may occur. For example, transient alterations in marker concentrations can occur after the commencement of chemotherapy (61–63). The spurious increases or spikes are probably attributable to therapy-mediated apoptosis or necrosis of tumor cells. Hayes et al. (62) reported a spike for either CA 15-3 or CEA in 7 of 16 patients undergoing chemotherapy. For CA 15-3, the peak of the spike above the initial value was 125% (range, 30%–230%), and its duration was 67 days (range, 31–101 days). All patients in whom a spike was observed ultimately showed either disease regression or had stable disease. In another study, spikes in CA 15-3 and CEA returned to pretreatment values by 60 days (63). As well as chemotherapy, treatment with granulocyte colony-stimulating factor can also cause increases in CA 15-3 concentrations (64).
- Certain benign diseases may give rise to increased marker concentrations. Thus, chronic active hepatitis, liver cirrhosis, sarcoidosis (65), hypothyroidism (66), and megablastic anemia (67) have all been reported to increase CA 15-3 concentrations.

Conclusion

The main disadvantages of existing serum markers for breast cancer are a lack of sensitivity for low-volume disease and a lack of specificity. Consequently, the available markers are of no value in either screening or diagnosing early breast cancer. Although of little use for early diagnosis, however, CA 15-3 may be the first independent circulating prognostic marker described for breast cancer. Preoperative CA 15-3 concentrations may thus be combined with established prognostic factors for use in deciding which lymph node-negative breast cancer patients should receive adjuvant chemotherapy. Currently, one of the most widely used applications of tumor markers in breast cancer is in the follow-up of patients with diagnosed disease. In the absence of data from a large randomized trial, however, the clinical value of this practice is unclear. Finally, markers are potentially useful in monitoring therapy in advanced disease, particularly in patients who cannot be assessed by standard modalities.

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