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ORIGINAL ARTICLE

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Long-term prognostic study of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in breast cancer

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Abstract
Background. Tumor markers are frequently used for screening and monitoring in oncology. We investigated the use of preoperative tumor marker (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 15-3) levels in estimating the prognosis of breast cancer patients.
Methods. We conducted a retrospective study in patients who underwent breast cancer surgery at National Cancer Center Hospital between 1975 and 1994 and whose serum CEA (n = 1663) and CA 15-3 (n = 1500) levels were measured prior to operation. When we excluded patients with stage IV disease from the study, the CEA level was within the normal range in 1470 patients, while 150 patients had an elevated CEA level. For CA 15-3, 1395 patients were within the normal range, while 70 patients exhibited an elevated level.
Results. The 5-year and 10-year survival rates for patients with normal CEA levels were 87% and 76%, respectively. However, the 5-year and 10-year survival rates for patients with elevated CEA levels were 76% and 65%, respectively. At both time points, patients with normal CEA levels had higher survival rates ($P < 0.05$). The 5-year and 10-year survival rates for the patients with normal CA 15-3 levels were 86% and 76%, respectively, while only 71% and 52% patients with elevated CA 15-3 levels survived at 5 and 10 years, respectively. These differences were also significant ($P < 0.05$). However, there were no significant differences in disease-free survival (DFS) according to CEA or CA 15-3 levels.
Conclusion. There was a positive correlation between CEA levels and CA 15-3 levels and patient prognosis. Thus, the levels of these tumor markers may help to determine prognosis in breast cancer patients.

Key words Breast cancer · Long-term survival · CEA · CA 15-3 · Retrospective study

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Introduction

Tumor markers, which are proteins or enzymes produced by tumor cells or generated by host cells in response to tumorigenesis, are frequently used for screening and monitoring in oncology. The expression of tumor-specific antigens varies, however, and, in general, tumor cells express several different unique antigens. Therefore, the most effective cancer screening protocols would combine multiple markers for increased specificity.

A number of tumor markers (e.g., carcinoembryonic antigen [CEA] and carbohydrate antigen 15-3 [CA 15-3]) are used clinically in the treatment of breast cancer, but the sensitivity of these markers is low, so that they are not useful as screening tools.[1] However, abnormally elevated levels of tumor markers prior to surgery in a patient with primary breast cancer suggest the presence of undetectable metastatic foci, and this is a negative prognostic factor. In addition, tumor marker levels tend to increase as tumor progression occurs; therefore, tumor markers, while of limited diagnostic use, are important for determining the prognosis of breast cancer.[1] In this study, we investigated the use of preoperative tumor marker (CEA and CA 15-3) levels in estimating the prognosis of breast cancer patients.

Patients and methods

We conducted a retrospective study in patients who underwent breast cancer surgery at National Cancer Center Hos-

Table 1. Characteristics of the patients

Stage	No. of patients							
	0	I	IIA	IIB	IIIA	IIIB	IV	Not known
CEA normal (n = 1495)	19	431	774	2	90	57	25	97
CEA high (n = 168)	1	29	69	1	24	22	18	4
CA15-3 normal (n = 1418)	18	413	744	3	80	49	23	88
CA15-3 high (n = 82)	0	4	32	0	13	20	12	1

pital between 1975 and 1994 and whose serum CEA and CA 15-3 levels were measured prior to operation. For serum CEA measurement, an enzyme immunoassay (EIA) was used until 1989 (n = 462), while a latex photometric immunoassay (LPIA) was used between 1990 and 1992 (n = 706). Until 1993, serum CA 15-3 was measured with a quantitative sandwich radioimmunoassay (RIA) utilizing two monoclonal antibodies (115D8, DF3; n = 1017). However, since 1993, a chemiluminescent enzyme immunoassay (CLEIA) has been used to measure both CEA and CA 15-3 (CEA, n = 495; CA 15-3, n = 483).

We set the criteria as follows. Normal values (thresholds) for CEA and CA 15-3 were set at less than 5.0 ng/ml and less than 28 U/ml, respectively. In this study, the CEA level was within the normal range in 1495 patients, while 168 patients had an elevated CEA level. As for CA 15-3, 1418 patients were within the normal range, while 82 patients exhibited an elevated level. When we excluded stage IV patients from the study, CEA level was within the normal range in 1470 patients, while 150 patients had an elevated CEA level. As for CA 15-3, 1395 patients were within the normal range, while 70 patients exhibited an elevated level. The clinical stages of the patients in each group are listed in Table 1. We used the Japanese Breast Cancer Society classification of breast cancer[2] for the stage classification.

Statistical analyses

The Kaplan-Meier method was used to calculate the cumulative survival rates for the different groups: CEA (normal and elevated levels), and CA 15-3 (normal and elevated levels). Statistical significance was tested using the log-rank test. P values of less than 0.05 were considered as significant.

Results

We found that the 5-year and 10-year survival rates for patients with normal CEA levels (n = 1470) were 87% and 76%, respectively. However, the 5-year and 10-year survival rates for patients with elevated CEA levels (n = 150) were 76% and 65%, respectively. At both time points, patients with normal CEA levels had higher survival rates (P < 0.05; Fig. 1). The 5-year and 10-year survival rates for the patients with normal CA 15-3 levels (n = 1395) were 86% and 76%, respectively, and only 71% and 52% patients with elevated CA 15-3 levels (n = 70) survived at 5 and 10 years, respectively. These differences were also significant (P < 0.05; Fig. 2). However, there were no significant differences in disease-free survival (DFS) according to either CEA or CA15- levels. The 5-year DFS rate in patients with normal CEA levels was 82%, and the rate in patients with elevated CEA levels was 73% (Fig. 3). The 5-year DFS rate in patients with normal CA 15-3 levels was 83%, and the rate in those with elevated CA 15-3 levels was 67% (Fig. 4).

We also performed a prognostic analysis of the levels of these tumor markers in relation to disease stage. In patients with stage II disease, those with normal CA 15-3 levels had

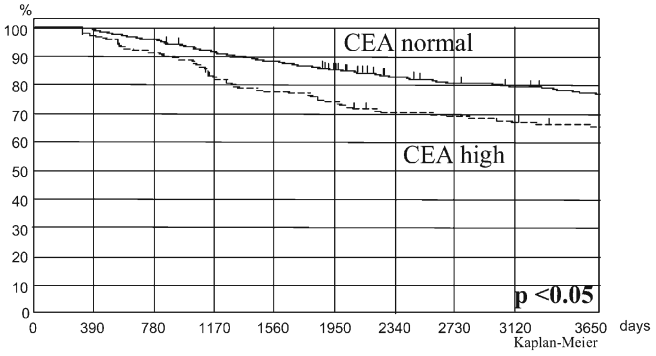

Fig. 1. The 5-year and 10-year survival rates for patients in relation to carcinoembryonic antigen (*CEA*) levels. *CEA normal* denotes normal CEA levels, and *CEA high* denotes elevated CEA levels

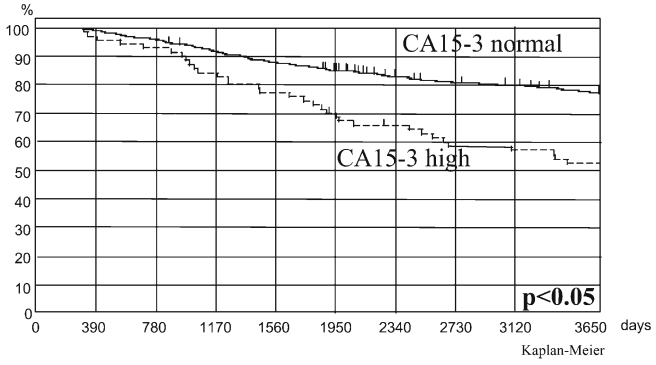

Fig. 2. The 5-year and 10-year survival rates for patients in relation to carbohydrate antigen 15-3 (*CA 15-3*) levels. *CA 15-3 normal* denotes normal CA 15-3 levels, and *CA 15-3 high* denotes elevated CA 15-3 levels

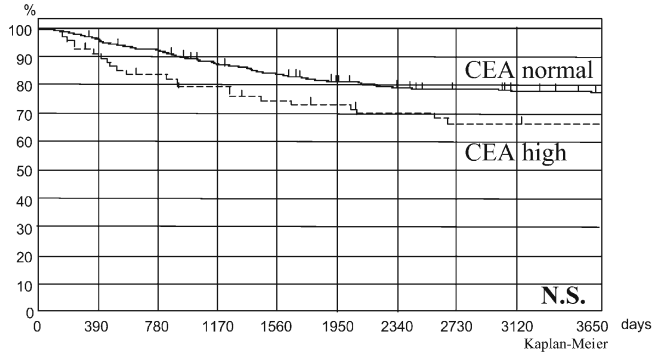

Fig. 3. Disease-free survival rates for patients in relation to CEA levels. *N.S.*, Not significant

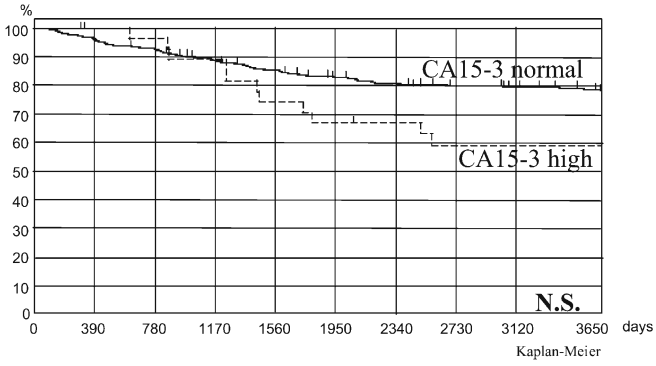

Fig. 4. Disease-free survival rates for patients in relation to CA 15-3 levels

a significantly better prognosis than those with elevated CA 15-3 levels. However, in patients with other disease stages, there was no significant difference in prognosis between those with normal levels and those with elevated levels of either tumor marker.

Discussion

During cellular transformation and progression to cancer, cancer cells release unique enzymes or proteins. Additionally, host cells can produce proteins in response to cancer. Such proteins are termed tumor markers and can be used to screen and monitor disease progression in oncology. Different tumor cells typically produce several unique tumor makers, and, while the specificity of any one marker may be low, the combination of several appropriate tumor markers is a powerful clinical tool.

Carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) are tumor markers commonly used in the screening for breast cancers. CEA is a glycoprotein that is overexpressed in various adenocarcinomas, while CA 15-3 is a mucin-like glycoprotein that is produced in stem cells in response to tumorigenesis.[1]

We conducted a retrospective study in breast cancer patients (excluding stage IV patients) treated at our hospital between 1975 and 1994, and investigated the relationship between CEA and CA 15-3 levels (measured at the time of first medical examination) and patient survival. Interestingly, the 5-year and 10-year survival rates of patients with normal CEA levels were 87% and 76%, while those of patients with elevated CEA levels were 76% and 65%, respectively. Thus, the prognosis of patients whose CEA level was within the normal range at the time of diagnosis was significantly better than the prognosis of those with elevated CEA levels (log-rank; $P < 0.05$). In addition, the 5-year and 10-year survival rates of patients with normal CA 15-3 levels were 86% and 76%, while these rates in the patients with elevated CA 15-3 levels were 71% and 52%, respectively. As with the CEA levels, the long-term survival of breast cancer patients with CA 15-3 levels within the normal range at the time of diagnosis was significantly better than the survival of patients with elevated CA 15-3 levels (log-rank; $P < 0.05$). Previous studies have identified an inverse relationship between tumor marker levels and prognosis when comparing patients with tumors of the same clinical stage.[3] Our results further demonstrate a relationship between preoperative tumor marker levels and long-term survival. Further work is needed to clarify which marker is superior for predicting prognosis, but both may be suitable. However, CA 15-3 may be more sensitive than CEA. The American Society of Clinical Oncology (ASCO) has reported that CA27-29, a MUC-1 marker, is better at tracking tumor recurrence than CA 15-3 (also a MUC-1 marker). Regardless of which marker is better, measuring the levels of MUC-1 markers is likely to be highly effective for monitoring tumor progression or recurrence.[1] Some studies have reported that tumor markers are effective for the early screening of recurrence,[4–7] but the sensitivity varies in these reports. Similar variation was observed when tumor markers were used in the diagnosis of primary breast cancer.[3,8,9] Of note, ASCO has reported that: (i) CEA is not recommended for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy (1997, 2000, 2007 recommendation); (ii) routine use of CEA for monitoring the response of metastatic disease to treatment is not recommended; and (iii) in the absence of readily measureable disease, elevated levels of MUC-1 markers (CA 15-3 and/or CA27-29) or a rising CEA level may suggest treatment failure.[1]

Significant differences in CA 15-3 expression levels between those in benign tumors and those in stage III and IV disease have been reported.[10] However, Gion et al.[11] reported that no differences were seen in CA 15-3 expression between benign tumors and stage I and II disease. Tumor marker levels tend to rise as disease progresses; therefore, tumor markers may be important prognostic factors.[1] Detecting elevated levels of preoperative tumor markers in patients with primary breast cancer may suggest the presence of undetectable metastatic foci; therefore, increased tumor marker levels are one factor that may predict a poor prognosis. Molina et al.[3,8] conducted a study of locoregional breast cancer and reported that the preoperative sensitivities of CEA and CA 15-3 were 11.7%–13% and 12.7%–18.8%, respectively. In addition, the sensitivities of CEA and CA 15-3 after recurrence were 30%–70%

Table 2. Past reports

Author	Year	No. of patients	Tumor marker	Sensitivity (%)	Patients state
Present study	2007	1620/1465	CEA, CA 15-3	CEA=9.11; CA 15-3=5.36	Preoperative
Soletormos[15]	2004	406	CEA, CA 15-3, TPA	CEA=or CA 15-3 or TPA=44–69	Recurrence
Molina[8]	2003	503	CEA, CA 15-3	CEA=11.7; CA 15-3=12.7	Locoregional breast cancer
Molina[3]	2003	1057	CEA, CA 15-3	CEA=13; CA 15-3=18.8	Locoregional breast cancer
Guadagni[9]	2001	2191	CEA, CA 15-3	CEA=16.7, CA 15-3=33.0, CEA+CA 15-3=39	Stage I–IV or metastatic disease
				CEA=38.5, CA 15-3=60, CA 15-3 and/or CEA=60	Recurrence
Lumachi[16]	2000	62	CEA, CA 15-3	CEA=40.3, CA 15-3=41.9, CEA+CA 15-3=59.7	Recurrence
Lumachi[17]	1999	103	CEA, CA 15-3	CEA=38.1, CA 15-3=61.1	Recurrence
Sutterlin[10]	1999	664	CEA, CA 15-3	CEA=30.3, CA 15-3=48.7	Recurrence
Molina[18]	1999	250	CEA, CA 15-3	CEA=31.6,CA 15-3=46.3, CEA+CA 15-3=59	Recurrence
Sutterlin[19]	1999	76	CEA, CA 15-3	CEA=30, CA 15-3=49,	Recurrence
Lauro[20]	1999	70	CEA, CA 15-3	CEA=35, CA 15-3=79, CEA+CA 15-3=79	Recurrence
Pectasides[21]	1996	68	CEA, CA 15-3	CEA=34, CA 15-3=68, CEA+CA 15-3=68	Recurrence
Jezersek[22]	1996	56	CEA, CA 15-3	CEA=70, CA 15-3=75	Recurrence

and 41.9%–79%, respectively (Table 2). In addition to well-known prognostic factors such as T-factor, N-factor, and hormone receptors, several references have acknowledged the relevance of tumor markers and prognosis.

In the present study, there were no significant differences in DFS according to preoperative levels of the tumor markers CEA and CA 15-3. Many studies have examined the relationship between recurrence and rising tumor marker expression levels. However, there is a delay between increases in marker levels and the confirmation of clinical recurrence, and this time period differs for each patient. In current practice, although a rise in marker expression may be detected, a patient will not be treated unless clinical recurrence is confirmed. A recent study compared the 7-year survival rates of patients undergoing surveillance treatment upon the detection of a rise in marker expression (n = 36) and those who were treated after the recurrence was confirmed by imaging (n = 32). Interestingly, tumor marker-guided salvage treatment prolonged the survival of the breast cancer patients.[12] However, a large-scale study conducted in 1320 postoperative breast cancer patients by the GIVIO investigators[13] found no significant differences in time to detection of recurrence between an intensive surveillance group and a control group. Furthermore, another study of postoperative breast cancer patients (n = 1243) found no difference in 5-year overall mortality between an intensive surveillance group and a control group.[14] Despite differences in the accuracy of current test methods, most studies have not found any differences in survival between groups undergoing intensive surveillance treatment for recurrence at an early stage and control groups; therefore, we believe that tumor marker-guided salvage treatment may not improve patient prognosis.

While tumor marker monitoring may not be useful for the detection of disease recurrence, our data support a role for CEA and CA 15-3 levels at least in helping to determine preoperative prognosis. We found that patients with elevated preoperative tumor marker levels had a significantly worse long-term prognosis than those patients with levels in the normal range. In relation to disease stage, stage II patients with normal CA 15-3 levels had a significantly better prognosis than those with elevated CA 15-3 levels. However, there were no significant differences in prognoses according to either CEA or CA 15-3 levels in patients with any other disease stage. This result suggested that the tumor marker level at the time of diagnosis was an independent prognostic factor. The early detection of recurrent foci may be accomplished using highly sensitive tumor markers, together with modern imaging technologies. Although the results of randomized controlled trials have demonstrated that the timing to initiate treatment for recurrence does not affect the overall survival rate, advances in imaging technology and improved treatment regimens may allow the early detection of recurrent foci and lead to improved patient survival. As diagnostic and treatment techniques improve, tumor markers will likely become more important in cancer therapy.

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