A Re-Evaluation of Carcinoembryonic Antigen (CEA) as a Serum Marker for Breast Cancer: A Prospective Longitudinal Study

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ABSTRACT

Purpose: Carcinoembryonic antigen (CEA) is still a widely used test for monitoring breast cancer, although recent reports discourage its routine use because of low sensitivity. This is a prospective study evaluating the efficacy of CEA and CA 15.3 in monitoring breast cancer.

Experimental Design: Serum CEA and CA 15.3 were measured in 2191 patients with either benign (n = 738) or malignant (n = 1453) breast diseases. Five hundred and forty-nine patients were monitored during postsurgical follow-up for either a minimum of 5 years or until time of recurrence. Fifty-three patients with metastases were also monitored during chemotherapy.

Results: Elevated CEA and CA 15.3 levels were found in 16.7% and 33.0% of patients, respectively. CEA sensitivity rose to 41.3% and CA 15.3 sensitivity rose to 80.8% in metastatic patients. The adjunct of CEA increased the CA 15.3 sensitivity by 6% in the overall population and by only 2.1% for patients with metastases. During postsurgical follow-up, CEA was elevated in 38.0% and CA 15.3 in 70.2% of patients with recurrence. The combination of CEA and CA 15.3 increased the overall sensitivity by only 1.4%.

Conclusions: CEA monitoring should be considered an expensive and inefficient method of follow-up evaluation for breast cancer patients, and it provides no additional value when used in combination with CA 15.3.

INTRODUCTION

CEA is one of the first tumor markers to be identified and characterized (1, 2). Since its discovery, CEA has been evaluated in a wide range of malignancies, including breast cancer, and, historically, has been considered the standard to which new serum markers are compared. Several studies have reported that positive serum CEA levels at the time of primary breast cancer diagnosis may represent a negative prognostic parameter (3–6) and correlate with the stage of disease (7–9). Several authors have shown that an increase or a decrease in the CEA levels may reflect the status of disease progression or regression (10–15). Literature suggests that CEA may be useful in the postsurgical follow-up of breast cancer patients for an early diagnosis of recurrence (16–21) and for monitoring response to treatment (22–24). It should be noted that the majority of these studies were performed 10–20 years ago. The availability of the CA 15.3 tumor marker in the last decade has greatly reduced the value of CEA in breast cancer management, and recent studies discourage the routine use of the CEA assay because of its low sensitivity in both early and advanced diseases (25–31) compared with CA 15.3 (25, 28–31). Nevertheless, CEA is still a widely used test for monitoring breast cancer patients.

This report presents the results of a prospective study conducted on more than 2000 patients diagnosed with either benign or malignant breast diseases. The study was designed to assess the usefulness of the CEA determination in comparison with that of CA 15.3 at the time of primary breast tumor, during postsurgical follow-up, and during chemotherapy. The problem of limited available financial resources, along with the rising cost of providing quality health care, results in the need to assess the cost effectiveness of various disease management protocols. Therefore, an economic evaluation was performed to assess the impact on cost and the effectiveness of the use or non-use of CEA in breast cancer and to provide an

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3 The abbreviations used are: CEA, carcinoembryonic antigen; INHS, Italian National Health Service; ROC, receiver operating characteristic; NS, not significant.
Patients and Methods

Patients’ Information. Two thousand one hundred and ninety-one consecutive patients with either benign (n = 738) or malignant (n = 1453) breast diseases, treated at our institutions between January 1991 and December 1994, entered into the study (Fig. 1). Benign diseases (fibrocystic disease, cysts, fibroadenomas, papillomas, inflammatory diseases, epithelial hyperplasia, and lipomas) were documented in all patients using diagnostic imaging and/or fine-needle aspiration or surgical biopsy.

The 1453 breast cancer patients [mean age, 58 ± 13 years (range 25–97 years); 446 (30.7%) premenopausal, 1007 (69.3%) postmenopausal] were histologically diagnosed with ductal (75.1%), lobular (11.6%), or other types (13.3%) of breast cancer, including medullary, tubular, papillary, mucinous, and mixed histotypes. Of the 1453 patients, those who entered into the study in the first 2 years of the recruitment [n = 549; mean age, 56 ± 12 years (range 25–83 years); 173 (31.5%) premenopausal, 376 (68.5%) postmenopausal; diagnosed with ductal (70.9%), lobular (15.5%) or other types (13.7%) of breast cancer] were also longitudinally monitored during postsurgical follow-up for either a minimum of 5 years or until time of recurrence. No significant differences were observed between this group of patients and the overall population. Three hundred and sixty-one patients remained clinically free of disease throughout the follow-up period, whereas 188 patients experienced a recurrence of disease. Of the patients with recurrent disease, 14 patients had local recurrence only, 20 had local recurrence followed by metastases, and 154 developed metastatic disease during longitudinal follow-up. Fifty-three of 174 patients who developed metastatic disease were monitored during chemotherapy (Fig. 1). Complete response was defined as the complete disappearance of all clinically evident disease; partial response was defined as a decrease > 50% of the sum of the largest diameters of all measurable lesions. An objective response, not satisfying the partial-response criteria, or a decrease of < 25% of the tumor mass was defined as no change. Progressive disease was defined as an increase of the sum of the largest diameters of measurable lesions or the appearance of new foci of metastatic disease. Clinical assessment of response was performed by the same multidisciplinary team.

Serum Collection and Tumor Markers Measurement. Blood samples from patients with primary breast cancer were drawn before surgery, at the time of each scheduled clinical follow-up, and monthly during chemotherapy. Sera from patients with advanced disease were obtained at the time of clinical diagnosis of recurrent disease and before any treatment. Blood samples from patients with benign disease were drawn at the time of fine-needle aspiration, at surgical videolaparotomy, or at the time of clinical diagnosis. All samples were aliquoted, coded, and stored at −40°C.

Serum CEA levels were measured by the CEA-RIA MAb kit (Abbott Laboratories, Inc., Chicago, IL) using the cutoff value of 5 ng/ml. Serum CA 15.3 levels were measured by the Centocor CA 15.3 RIA kit (Fujirebio Diagnostics Inc., Malvern, PA) using the cutoff value of 30 units/ml. Intra- and interassay variations for both markers were < 5% and < 10%, respectively. Measurement of serum CEA and CA 15.3 was done blinded. All samples above the standard curve were retested with appropriate dilutions. An increase in the serum marker levels was considered significant either when negative (below the cutoff value) serum levels became positive (above the cutoff value) or when an increase of > 50% of the mean of the two previous positive levels was detected.

Statistical Analysis. Antigen levels are expressed as the mean ± SD or median and ranges. Differences between groups were assessed using the Mann-Whitney nonparametric U test. Only Ps < 0.05 were regarded as statistically significant. ROC curves were drawn for CEA and CA 15.3 based on true-positive and false-positive ratios. Significant differences in test performances were calculated from the area under the curve according to the technique described by Hanley and McNeil (32). All calculations were made using a computer software package (Systat 8.0).

Results

Sensitivity and Specificity. Serum samples obtained from 1453 patients with primary (1155), locally recurrent (58), or metastatic (240) breast cancer were analyzed for the presence of CEA and CA 15.3. Elevated CEA and CA 15.3 levels were found in sera from 242 (16.7%) and 480 (33.0%) of 1453 patients with breast cancer, respectively (Table 1). Furthermore, CEA was able to identify only 99 of 240 (41.3%) patients with metastatic breast cancer, whereas CA 15.3 detected ~ 81% of these cases (Table 1).

A comparison between the two markers is summarized in Table 2. As shown, the addition of CEA measurement to that of CA 15.3 alone was capable of adding only a 6% increase in
Table 1  Specificity and sensitivity of serum CEA and CA 15.3 levels in patients with breast disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Serum marker levels&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CA 15.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CEA (&gt;5 ng/ml)</td>
<td>CA 15.3 (&gt;30 units/ml)</td>
</tr>
<tr>
<td>Benign</td>
<td>738</td>
<td>21 (2.9)</td>
<td>58 (7.9)</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>392</td>
<td>25 (6.4)</td>
<td>48 (12.2)</td>
</tr>
<tr>
<td>II</td>
<td>562</td>
<td>63 (11.2)</td>
<td>124 (22.1)</td>
</tr>
<tr>
<td>III</td>
<td>153</td>
<td>35 (22.9)</td>
<td>56 (36.6)</td>
</tr>
<tr>
<td>IV</td>
<td>48</td>
<td>12 (25.0)</td>
<td>30 (62.5)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>240</td>
<td>99 (41.3)</td>
<td>194 (80.8)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>58</td>
<td>8 (13.8)</td>
<td>28 (48.3)</td>
</tr>
<tr>
<td>Total</td>
<td>1453</td>
<td>242 (16.7)</td>
<td>480 (33.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Numbers in parentheses represent percentages.

sensitivity to the overall population. No additional increase in sensitivity was obtained by combining the two markers in stage IV primary breast cancer, whereas the addition of CEA increased the percentage of positive patients with metastatic or locally recurrent breast cancer by only 2.1 and 3.4%, respectively.

A total of 288 patients had metastatic breast cancer (48 had stage IV primary breast cancer, and 240 entered the study at time of first diagnosis of metastatic disease). The percentages of CEA- and CA 15.3-positive serum levels in patients with metastatic breast cancer by site metastases are summarized in Table 3. Positive CEA and CA 15.3 serum levels were found in 2 (20%) versus 6 (60%) of 10 patients with skin metastases, 7 (18.4%) versus 23 (60.5%) of 38 patients with lymph node metastases, 47 (38.2%) versus 93 (75.6%) of 123 patients with bone metastases, and 55 (47.0%) versus 102 (87.2%) of 117 patients with visceral metastases (Table 3). Moreover, 23 (50.0%) and 40 (87.0%) of 46 patients with liver metastases had elevated serum CEA and CA 15.3 levels, respectively. The addition of CEA increased the percentage of positive patients with bone and visceral metastases by 1.6% and 3.4%, respectively (Table 3).

ROC curves of CEA, CA 15.3, and a combination of the two in the overall population (1453 malignant versus 738 benign breast diseases) are drawn in Fig. 2. As shown, CEA (Fig. 2A) had worse curve characteristics than CA 15.3 (Fig. 2B). The area under the ROC curve, in fact, was 0.57 for CEA versus 0.70 for CA 15.3 (P < 0.0001). Moreover, when CEA was added to CA 15.3, the overall test performance was greatly reduced (ROC area, 0.61; P < 0.02; Fig. 2C). Similar results were obtained when considering only patients with advanced breast cancer (data not shown).

Longitudinal Monitoring. Five hundred and forty-nine of 1453 patients, who entered into the study in the first 2 years of the recruitment, were longitudinally monitored during post-surgical follow-up for either a minimum of 5 years or until time of recurrence. As shown in Table 4, 361 (65.8%) of the 549 patients remained free of disease throughout follow-up; no significant elevations of either CEA or CA 15.3 were found in this group at any time. Recurrent disease was observed in 188 patients, for a total of 208 recurrences, including local recurrence (n = 34) and skin (n = 6), lymph node (n = 28), bone (n = 72), and visceral (n = 68) metastases. Overall, serum CEA and CA 15.3 levels were elevated in 38.0% (79 of 208) and 70.2% (146 of 208) of recurrent diseases. Serum CEA levels were elevated in only 14.7% (5 of 34) of local recurrences, whereas CA 15.3 levels were elevated in ~44% of the cases. Moreover, increased CEA and CA 15.3 serum levels were found in 2 (33.3%) versus 4 (66.6%) of 6 cases of skin metastases, in 5 (17.9%) versus 16 (57.1%) of 28 cases of lymph node metastases, in 34 (47.2%) versus 55 (76.4%) of 72 cases of bone metastases, and in 33 (48.5%) versus 56 (82.4%) of 68 cases of visceral metastases (Table 4). The increase in sensitivity obtained by adding CEA determination to that of CA 15.3 alone ranged from 0.0% in the case of bone metastases to 4.4% in the case of visceral metastases, yielding to only a 1.4% increase in the overall sensitivity (Table 4).

Of 174 patients who developed metastatic disease, 53 were longitudinally monitored during chemotherapy. Serum CEA and CA 15.3 levels were elevated in 15.1% (8 of 53) and 39.6% (21 of 53) of patients, respectively, before surgery for primary disease (Table 5). Median CEA and CA 15.3 levels were 2.2 ng/ml and 26 units/ml, respectively. At the time the metastases were first diagnosed, CEA and CA 15.3 median levels were 4.7 ng/ml (P < 0.002) and 68.1 units/ml (P < 0.0001), respectively. The metastases were found to progress during chemotherapy in 31 patients. In this group, serum CA 15.3 and CEA levels increased in 22 (70.9%) and 12 (38.7%) patients, respectively. When positive, both markers continuously increased in this group. In fact, the median CA 15.3 level was 130.1 units/ml (P < 0.05), whereas the median CEA level was 5.2 ng/ml (P = NS). The metastases regressed in 17 patients, as evidenced by imaging techniques, and there was a corresponding decrease of both CA 15.3 [13 of 17 (76.5%); median, 39.2 units/ml (P < 0.05)] and CEA [8 of 17 (47.1%); median, 2.4 ng/ml (P < 0.05)]. In the remaining five patients, the extent of metastases did not change during chemotherapy. Accordingly, serum markers did not show any substantial change, with the only exception being one patient whose CEA levels decreased from 6.0 to 3.9 ng/ml. In this group, CA 15.3 and CEA median values were 121.6 units/ml (P = NS) and 7.6 ng/ml (P = NS), respectively.

Cost Projections. Considering the INHS’s interest in economic evaluation, we analyzed the ability of serum CEA and CA 15.3 to detect tumors in patients with breast cancer as the effectiveness end point (33). To calculate total costs, we acquired information about the price paid by INHS for CEA and CA 15.3 tumor markers (37,000 Italian liras each Euro). On the basis of the data collected in this study, we calculated the cost of using serum CEA for a 5-year follow-up. Even if there is no evidence for the real effectiveness in using tumor markers in the follow-up of breast cancer patients, in Italy.
as well as in other advanced countries, there is a consolidated custom of requiring CEA and CA 15.3. Therefore, each time that a physical examination is recommended, we could hypothesize that physicians tend to perform a CEA test (three times/year in the first 3 years after surgery, thereafter two times/year in the following 2 years, for a total of 13 tests). Consequently, the total number of CEA tests for each patient in a 5-year follow-up would add up to 15 (including pre- and postsurgery tests), with a total cost of 286.65 Euro/patient (19.11 Euro/H11003 15).

On the basis of these calculations, an estimate of the cost for a 5-year follow-up of the 549 patients enrolled into the present study would be 157,371 Euro (549 H11003 286.65 Euro).

Therefore, from the results reported in Table 4, a cost-effectiveness ratio of 1992 and 1078 Euro/recurrence detected by CEA and CA 15.3, respectively, can be calculated. The combined evaluation of serum CEA and CA 15.3 levels during follow-up pointed out an overall increase in sensitivity (using CEA in addition to CA 15.3) of 1.4% (Table 4). Thus, CEA helped in the detection of recurrent disease in only five cases. This suggests a cost-effectiveness ratio of 31,474 Euro/each recurrence detected by the addition of CEA to CA 15.3.

To give an idea of the economic impact of CEA use at a health service macro-level, we also estimated the cost of CEA use in the INHS. For this reason, using data from the Ministry of Health (Department of Health Care Planning), we calculated the number of patients who, in 1996, were treated for breast cancer. Using the disease-related group (DRG) classification system we considered surgical patients undergoing either total or subtotal mastectomy for breast cancer, with or without surgical complications (n = 34,717 in 1996). For all these patients we can reasonably consider a typical pattern of use of tumor markers as stated above, which provides an estimated total cost of 9,951,628 Euro for CEA for the INHS for patients who, in 1996, had surgical treatment for breast cancer. This cost is relative to a 5-year follow-up, although it is reasonable to hypothesize that each year a similar number of patients will be present in the same DRGs. For this reason the calculated total cost of 9,951,628 Euro can be considered as an annual cost for the INHS.

DISCUSSION

The results obtained in this prospective study clearly demonstrate the lack of utility of CEA measurement compared with CA 15.3. CEA sensitivity was significantly lower compared with that of CA 15.3 (Table 1). Moreover, the adjunct of CEA to CA 15.3 measurement resulted in only a minimal improvement of the sensitivity (ranging from 1.9% in metastatic patients to 6% in the overall population; Table 2). The results obtained using the ROC analysis demonstrated that the addition of CEA to CA 15.3 measurement reduced the level of significance of the CA 15.3 test (Fig. 2).

As stated above, a 6% increase in sensitivity was observed in the overall population, which means that 87 women might have taken advantage from CEA determination during postsurgical follow-up. However, the findings obtained in the postsurgical follow-up of 549 patients provided additional support for the concept that CEA should not be used to monitor the recurrence of breast cancer. Of 188 patients who had recurrent disease, in fact, only 38% showed positive CEA levels compared with 70% monitored by CA 15.3 (Table 4). Furthermore, the increase in sensitivity achieved by combining CEA and CA 15.3 measurements was not significant (1.4%). A comparison of the two tumor markers during chemotherapy of metastatic patients confirmed that CA 15.3 is, indeed, more informative than CEA. A prospective study using CA 15.3 as a discriminator of two populations after the patient has received...
two courses of chemotherapy should be performed to define a
technique that shows therapeutic response and another popula-
tion which has not responded to the chemotherapy. This may be
the most important role for CA 15.3 in monitoring patients
with breast cancer who are receiving first-line chemotherapy.

At the present time we cannot conclusively define the
clinical impact of CA 15.3 determination in the management of
breast cancer patients. The American Society of Clinical On-
ology guidelines (34) state that there is insufficient data to
recommend the use of serum tumor markers. Although the
tumor marker is able to detect the recurrence of disease before
clinical or diagnostic imaging modalities, there is no data avail-
able to prove that this results in an increase in overall survival
and/or quality of life. This lack of demonstrable improved
survival is primarily attributable to the lack of effective second-
time line therapy and not the result of tumor markers. Indeed, at
the present time there is no effective therapy available to salvage
patients who develop recurrent disease after definitive therapy.
Until such therapies become available, early detection of the
disease has little impact on survival. However, if effective
therapies become available, even a small percentage of addi-
tional patients in whom disease could be detected early may
play an important role.

The present study does not support the recommendation
given in the American Society of Clinical Oncology clinical
practice guidelines for the use of tumor markers in breast cancer.
Their recommendation is, “to choose, when both CEA and CA
15.3 are elevated, the least expensive alternative (CEA at the
present time)” (34). Our results demonstrate an extremely low
sensitivity of CEA in breast cancer patients. Even in those cases
showing positive CEA levels, the amount of antigen in almost
all of the patients was much lower that that of CA 15.3 (Table
5) and, therefore, of less clinical value. CEA alone was positive
only in an extremely low percentage of cases, invalidating its
possible use in combination with CA 15.3.

To be cost effective, it is necessary to select tests that
provide the most significant clinical information. In an effort to
control costs, tests that are of limited value should not be used
in patient management. In this study, we looked at the impact on
costs and effectiveness of the use-non use of CEA tumor marker
in breast cancer, providing an estimation of economic impact of
CEA use for the INHS. Although the cost of CEA serum assay
may vary among countries, given the low sensitivity of CEA in
monitoring breast cancer patients, it appears to be unjustified.

In conclusion, our prospective study shows the lower sen-
sitivity of serum CEA levels compared with CA 15.3 assay in
detecting breast cancer. The study also provided evidence for
recommending that serum CEA should not be used in the
management of this disease. A randomized prospective study

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Serum marker levels&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Increase in sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NED&lt;sup&gt;b&lt;/sup&gt;</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>Recurrent disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>34</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>28</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Bone</td>
<td>72</td>
<td>34 (47.2)</td>
</tr>
<tr>
<td>Visceral</td>
<td>68</td>
<td>33 (48.5)</td>
</tr>
<tr>
<td>Total</td>
<td>208</td>
<td>79 (38.0)</td>
</tr>
<tr>
<td>Serum marker levels&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA (&gt;5 ng/ml)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CA 15.3 (&gt;30 units/ml)</td>
<td>15 (44.1)</td>
<td>16 (47.1)</td>
</tr>
<tr>
<td>CEA and/or CA 15.3</td>
<td>0 (0.0)</td>
<td>16 (47.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Numbers in parentheses represent percentages.
<sup>b</sup> NED, no evidence of disease; NA, not applicable.

Table 5 Serum CEA and CA 15.3 levels in 53 patients undergoing chemotherapy for recurrent breast adenocarcinoma

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Serum CEA levels</th>
<th>Serum CA 15.3 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presurgery&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. positive (%)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>53</td>
<td>8 (15.1)</td>
<td>3.5 ± 6.9</td>
</tr>
<tr>
<td>Metastases&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53</td>
<td>20 (37.7)</td>
</tr>
<tr>
<td>PD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>NC</td>
<td>5</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>3 (17.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mann-Whitney nonparametric U test between antigen levels at the time of diagnosis of metastatic disease and during therapy.
<sup>b</sup> Surgery of primary breast cancer.
<sup>c</sup> First diagnosis of metastasis.
<sup>d</sup> P < 0.002.
<sup>e</sup> P < 0.001.
<sup>f</sup> PD, progression of disease; NC, no change.
<sup>g</sup> P < 0.05.
<sup>h</sup> Including partial or complete responses to chemotherapy.
should be performed to assess the clinical impact of other serum tumor markers, particularly CA 15.3.

REFERENCES


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