A re-evaluation of carcinoembryonic antigen (CEA) as a serum marker for breast cancer: a prospective longitudinal study


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of carcinoembryonic antigen (CEA) for monitoring breast cancer at three different stages. The three stages were at the time of diagnosis of the primary tumour, during the post-surgical follow-up and during chemotherapy.

Type of intervention
Other: staging and monitoring of disease.

Economic study type
Cost-effectiveness analysis.

Study population
There were effectively three studies reported in this paper, each with a different population.

At the time of diagnosis of the primary tumour, the study population comprised breast disease patients, both with benign (i.e. fibrocystic disease, cysts, fibroadenomas, papillomas, inflammatory diseases, epithelial hyperplasia, and lipomas) and malignant diseases.

During the post-surgical follow-up, the study population comprised breast cancer patients with malignant disease (pre- or postmenopausal) who had undergone surgery.

During chemotherapy, the study population comprised breast cancer patients who had developed metastatic disease and were undergoing chemotherapy.

Setting
The setting appears to have been secondary care. The economic study was performed in Rome, Italy.

Dates to which data relate
The effectiveness and cost data appear to have been collected between January 1991 and December 1997. The price year was not reported.

Source of effectiveness data
The effectiveness data came from three consecutive studies.

Link between effectiveness and cost data
The cost data seem to have been collected on the same patient population as that used for the effectiveness analysis. However, the authors did not report whether the costing was carried out prospectively or retrospectively.
**Study sample**

No power calculations were reported to have been performed in the planning phase for each study to assure a certain power.

Study 1 (primary tumour diagnosis) recruited patients from the authors’ institutions. In total, 738 patients had benign breast diseases and 1,453 had malignant breast diseases.

Study 2 (post-surgical follow-up) recruited patients from the 1,453 patients with malignant breast disease. A total of 549 patients with malignant breast disease were eligible for follow-up. To be eligible for follow-up, the patients had to have been recruited during the first 2 years of the study.

Study 3 (chemotherapy) recruited patients from the 549 patients with malignant disease who developed metastatic disease. These numbered 174, of whom 53 were followed-up and the rest were lost to follow-up.

**Study design**

This was a multi-centred, diagnostic cohort study, although the number of centres that participated was not reported. The three consecutive studies were performed on population subsets (described above). Tests for CEA and CA 15.3 were carried out on each patient. The period of follow-up for the 549 who underwent surgery was 5 years or until recurrence of disease. The authors reported that the serum levels of CEA and CA 15.3 were measured in a blinded fashion. It appears that 121 of the 174 patients with distant recurrent malignant disease who received chemotherapy were lost to follow-up at some point during the 5-year follow-up period.

**Analysis of effectiveness**

The health outcomes assessed in study 1 were:

the number of patients in the total sample who had either benign disease, malignant disease (stages I, II, III and IV), metastatic disease or local recurrence;

the number (and percentages) of breast cancer patients with positive CEA and CA 15.3 serum levels, and the increase in the sensitivity of CA 15.3 by an additional CEA test;

the number of patients with metastatic breast adenocarcinoma by site of metastasis (either cutis, lymph nodes, bone or visceral metastasis), and the number (and percentages) of these patients with a positive serum level as detected by CEA, CA 15.3 and CEA combined with CA 15.3; and

the number of visceral metastatic patients whose metastases were limited to the liver, and the number (and percentage) of them who had positive CEA, CA 15.3 and CEA combined with CA 15.3.

The health outcomes assessed in study 2 were, for those patients with breast adenocarcinoma who were followed up after surgery:

the number of them with no evidence of disease, and the number of them with recurrent disease (either local recurrence, skin, lymph nodes, bone, or visceral adenocarcinoma);

the number (and percentages) of them who obtained positive CEA, CA 15.3 and CEA combined with CA 15.3; and

the increase in sensitivity for each one of these groups when CA 15.3 was performed, in comparison with CEA.

The health outcomes assessed in study 3 were, for patients with recurrent breast adenocarcinoma who were followed up after chemotherapy:

the number of them who had undergone prior surgery of primary breast cancer, had metastases, experienced progression of disease, did not change, and responded to chemotherapy;
the number (and percentages) of them who had positive CEA and CA 15.3 serum levels; and
the mean, standard deviation, median and ranges for each of the serum CEA and CA 15.3 levels.

There was no need to show that the groups were comparable at analysis, as the same patient group was tested with both CEA and CA 15.3 tests.

**Effectiveness results**

Only a summary of selected effectiveness results is reported here.

In study 1, of the 738 patients with benign disease, a CEA level of greater than 5 ng/mL was detected in 21 (2.9%) and a CA 15.3 level of greater than 30 units/mL was detected in 58 (7.9%). The corresponding values for the 1,453 patients with malignant disease were 242 (16.7%) for CEA (>5 ng/ml) and 480 (33%) for CA 15.3 (>30 units/mL).

For study 2, of the 361 cases with no evidence of disease, none were found with the above levels of CEA (>5 ng/mL) and CA (>30 units/mL). Of the 208 patients with a recurrent disease, a CEA level of greater than 5 ng/mL was detected in 79 (38%) and a CA 15.3 level of greater than 30 units/mL was detected in 146 (70.2%).

For study 3, of the 31 patients whose metastases were found to progress, the serum CEA levels gave a positive result for 18 (58.1%) while the serum CA 15.3 levels gave a positive result for 27 (87.1%).

**Clinical conclusions**

The results demonstrated a lack of utility of CEA measurement in comparison with CA 15.3. The sensitivity of CEA was significantly lower than that of CA 15.3 at the time of diagnosis of the primary tumour. The combination of CEA and CA 15.3 resulted in only a minimal improvement. The sensitivity of CA 15.3 was again higher for the post-surgical and chemotherapy analyses.

**Measure of benefits used in the economic analysis**

The measure of health benefit used in the economic analysis was the number of recurrences detected in the overall population by CEA, CA 15.3 and by the addition of CEA to CA 15.3.

**Direct costs**

Only the number of tests performed during the 5-year follow-up period, but not any other resource utilisation, was reported separately from the costs. The direct costs included in the analysis were those of the monitoring procedures. The price paid by the Italian National Health Service (INHS) for CEA and CA 15.3 was used as a proxy for costs. Therefore, the costs were estimated from actual data. The price paid for both procedures was reported to be the same. Discounting was not reported to have been performed, although it was relevant since the costs were incurred over more than 2 years. The study reported the unit costs for the tests, and the total costs for the tests performed during the 5-year follow-up period. The date to which the price data referred was not reported.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

No indirect costs were reported.

**Currency**

Italian lira (L) and Euro.
Sensitivity analysis
No sensitivity analysis was conducted on the cost-effectiveness results.

Estimated benefits used in the economic analysis
The number of recurrences detected in the overall population was 79 with the CEA test, 146 with the CA 15.3 test, and 151 with the combination of CEA and CA 15.3. Therefore, 5 additional cases of recurrent disease could be detected by adding CEA to the CA 15.3 test. The benefits were estimated for a 5-year period.

Cost results
The total cost of the CEA test per patient during the 5-year follow-up period considered at analysis was Euro 282.65. The total cost of CEA for the whole group of 549 patients that were followed up during this period was Euro 157,371. The costs per patient and for the whole group were the same for the CA 15.3 test, since the authors reported that the price paid by the INHS were the same for both procedures. The costs of adverse events, such as those generated in patients with false positive test results, were not dealt with in the economic analysis.

Synthesis of costs and benefits
The average cost-effectiveness ratios (CER) were calculated as the cost per case of recurrent disease detected with CEA and CA 15.3. An incremental cost-effectiveness ratio (ICER) was also calculated as the incremental cost of combining the CEA and CA 15.3 tests per additional case of recurrent disease detected, in comparison with CA 15.3 alone.

The CERs were Euro 1,992 per case of recurrent disease detected with CEA, and Euro 1,078 per case of recurrent disease detected with CA 15.3.

The ICER for the combination of CEA and CA 15.3, compared with CA 15.3 alone, was Euro 31,474 per case of recurrent disease detected.

Authors' conclusions
The results of the study clearly demonstrated the lack of utility of carcinoembryonic antigen (CEA) measurement when compared with CA 15.3, due to its significantly lower sensitivity and the minimal improvement in sensitivity obtained when it was combined with CA 15.3. No definite conclusion about the utility of CA 15.3 for the management of breast cancer patients was drawn. This is because, as the authors stated, although CA 15.3 may detect disease recurrence before clinical or diagnostic modalities, there is no information available about the impact of this on overall survival and/or quality of life. This is primarily because of the lack of an effective therapy for recurrent disease.

CRD COMMENTARY - Selection of comparators
The comparator, CA 15.3, was justified on the grounds that it was current practice in the authors' setting, besides CEA. In addition, it had better sensitivity. You should consider if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis used a diagnostic cohort study, which seems to have been appropriate for the study question. The authors did not provide evidence that each study sample was representative of the relevant study populations. However, the fact that more than one centre was considered in the effectiveness analysis may have increased the likelihood of the study samples being representative of the study populations. No power analysis was reported.

Validity of estimate of measure of benefit
The measure of benefit used in the economic study was the number of recurrences detected by the tests. It was obtained directly from the effectiveness analysis. This choice of estimate was not justified.
Validity of estimate of costs
The perspective adopted was not reported, but it seems to have been the health service. The only costs considered at analysis were those of the CEA and CA 13.5 tests. No statistical analyses were performed. Moreover, prices paid by the INHS were used as a proxy for the costs, which may not reflect the true opportunity costs of the CEA and CA 13.5 procedures. The authors did not state which categories of costs were included in this price. These facts introduce uncertainty into the reliability of the conclusions. The price year was not reported, which hinders reflation exercises to other settings.

Other issues
The authors did not make appropriate comparisons of their findings with those from other settings. The issue of generalisability of the results to other settings was mentioned. The authors stated that, although the costs of CEA serum may vary among countries, the expense does not appear to be justified given its low sensitivity. The authors’ conclusions reflected the scope of the analysis. The results were reported in full.

Implications of the study
The authors recommend that serum CEA should not be used in the management of breast cancer. As they state, a prospective study should be performed to assess the clinical impact of other serum tumour markers. In particular, using CA 15.3 as a discriminator of two populations after the patient has received two courses of chemotherapy, in order to define populations showing or not showing therapeutic response.

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Other publications of related interest


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