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Serum Carcinoembryonic Antigen in the Diagnosis and Prognosis of Women with Breast Cancer

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Abstract—*Serum carcinoembryonic antigen (CEA) has been measured in 628 patients before and 577 patients after treatment for breast cancer. These came from an unselected sequence of 730 women, subsequently diagnosed as having stage I or II breast cancer, referred to Guy's Hospital over a period of nearly 5 yr. CEA was also measured in serum from 238 ostensibly healthy volunteers and 65 women with benign breast disease. CEA measurements were of no diagnostic value. There were more patients with breast cancer with values in excess of 10 ng/ml measured pre-operatively (7%) or after mastectomy (5%) than in controls (3%), but the difference is of marginal significance. High levels of CEA were not consistently associated with pathological stage or histological grade. Mastectomy was not associated with any significant change in the distribution of CEA levels. Patients with stage II disease and pre-operative CEA levels over 10 ng/ml has a faster recurrence rate than those with levels of less than 2.5 ng/ml. High levels were also associated with reduced survival. However, such patients comprised about 5% of women presenting with early breast cancer, so that the use of CEA measurements for prognosis is of limited value.*

INTRODUCTION

THERE has been considerable controversy over the use of measurements of carcinoembryonic antigen (CEA) as a prognostic indicator in patients with breast cancer [1–10]. This has arisen, in part, because various investigators have had widely different aims. Some have hoped to use CEA assays as an index of tumour burden [2, 11–13]; others have concentrated on the biological properties of the tumour in terms of growth rates [2, 4, 5, 7, 10] or response to endocrine treatment or chemotherapy [3, 6, 10, 14–18]. To complicate the matter further, the time at which the blood specimens were obtained before and after treatment and the frequency with which serial specimens are obtained has varied widely. On the technical side there have been few attempts to standardize antisera, and statistical evaluation of results have sometimes fallen short of the recommendations of de Jong-Bakker *et al.* [19].

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Under these circumstances it is difficult to generalize about the potential value of CEA assays as a prognostic tool, and it would seem sensible that each centre should determine their usefulness in their own particular local circumstances. This report is concerned with the relation between serum CEA levels, measured immediately before and shortly after mastectomy, and subsequent recurrence rates in patients from Guy's Hospital London. In addition, the diagnostic value of CEA measurements has been assessed by comparing results in breast cancer cases with those from an ostensibly normal population.

MATERIALS AND METHODS

Subjects

The study was based on a sequential series of 730 unselected patients with stage I or stage II breast cancer who had been referred to Guy's Hospital between February 1975 and December 1979. The statistical analysis was done on a final follow-up dated February 1982, when the median follow-up was 41 months (range 1–88 months).

During this period 139 patients had a recurrence of their disease, with a median time to recurrence of 19 months (range, 1–68 months). The control subjects were 238 women living on the island of Guernsey who were ostensibly healthy and who had volunteered to give blood during 1977–1978. The 65 women with benign breast disease shown in Table 1 had attended Guy's Hospital in 1979.

The characteristics of these three groups are given in Table 1.

Pathological stage and histological grade

The stage of breast cancer at presentation was determined using the TNM staging protocol [20]. Histological grade (1–3) was assessed by a method based on the criteria of Bloom and Richardson [21].

Blood samples

Blood samples were taken from patients with breast cancer the morning before and 10 days after surgery. The choice of taking blood at these times was governed primarily by the welfare of the patient and the smooth running of the Breast Unit at Guy's Hospital. Blood specimens taken earlier than 1 day before surgery would have meant earlier admittance to hospital. The post-operative specimens were taken at 10 days since this represented a time just prior to discharge from hospital for most patients—giving a maximum time for patients to recover from the effects of surgery. For women with benign breast disease the blood was taken before biopsy. Normal control volunteers were bled either in the afternoon or early evening. After clotting and centrifugation, the serum was separated and divided into aliquots. Sera was stored at -20°C until analysed.

CEA analysis

Serum CEA was measured using a polyethylene glycol-assisted double-antibody radioimmunoassay. The antibody and CEA standards were gifts from Dr. J. P. Persijn and the method was essentially that used by him [22]. The antibody was raised against CEA obtained from liver metastases of a colonic tumour. Quality controls at 2 levels of CEA were included in each batch of samples assayed. The coefficient of variation of these pools over the study was 15 and 14% [mean titre, 17.5 and 8.6 ng/ml respectively; $n = 36$ in both cases]. The lower limit of detection with this method is 2.5 ng/ml. CEA was measured in 628 and 577 serum samples collected before and after treatment respectively. Of the 730 patients, 688 (94%) had at least one CEA measurement and 517 (71%) had both values.

Statistical analysis

Recurrence rates were analysed using the log rank test described by Peto *et al.* [23, 24]. The distribution of CEA between groups was compared using Fisher's exact probability test. This test was used rather than χ^2 because of small numbers in some of the groups.

RESULTS

Diagnosis

Distribution of CEA values in controls and patients with benign disease. The CEA values have been divided into four categories as described by de Jong-Bakker *et al.* [19]: $\leqslant 2.5, 2.6–5.0, 5.1–9.9$ and $\geqslant 10$ ng/ml. The number of controls and patients with benign disease whose values fall into these categories are shown in Table 2, and it is quite obvious that the distribution of the values is almost identical in the two groups of women.

Table 1. Characteristics of subjects

	Controls	Benign disease	Breast cancer
No.	238	65	730
Pre-menopausal	113	38	252
Menopausal	23	5	88
Post-menopausal	91	17	351
Unknown	11	15	39
Median age	46	38	54
(Range)	(31–74)	(15–64)	(23–91)
Clinical			
Pathological stage 1	—	—	379
Pathological stage 2	—	—	313
Not determined	—	—	38
Histological grade 1	—	—	176
Histological grade 2	—	—	293
Histological grade 3	—	—	175
Not determined	—	—	86

Pre-operative levels in patients with breast cancer. When all patients with breast cancer are compared with controls (Table 3), a similar distribution of CEA values is found, except that there is a greater proportion of patients with values above 10 ng/ml than in the controls (7 and 3%; $P = 0.02$).

The results were then re-analysed for various sub-sets of patients to determine whether high values were concentrated into any particular stage or grade category. The results are shown in Table 3, and in stage I patients or in grade 3 patients there was a significantly greater proportion of high values compared with controls ($P < 0.01$; $P < 0.02$). However, these levels of significance should be viewed against the number of statistical tests performed (see ref. [12]).

Post-operative levels. There is no significant difference in the distribution of values in patients after mastectomy compared with controls, although once again there is a small excess of high values (5 vs 3%) (Tables 2 and 4). In the sub-sets of patients, the only significant difference was found in those with grade 3 tumours (6 vs 3%; $P = 0.04$).

The number of patients with CEA levels in excess of 20 ng/ml, the 'highly increased' category of de Jong-Bakker, was extremely small: 3 out of 628 and 4 out of 577 measured pre- and post-operatively respectively. This category is therefore only of relevance in patients with advanced metastatic disease.

It is quite clear from the results in this and in the preceding section that CEA measurements have no diagnostic value.

Prognosis

Recurrence rates after mastectomy. Patients were sub-divided according to either stage or grade and recurrence rates were compared for 4 categories of patients: women with serum CEA <2.5, 2.6–5.0, 5.1–9.9 and ≥10 ng/ml. There were no significant differences in the rates of recurrence between any of these categories except for patients with stage 2 disease and CEA values measured before operation; in this particular case women with 10 ng/ml or more of CEA had significantly faster rates of recurrence than patients with CEA less than 2.5 ng/ml ($P < 0.025$), as shown in Fig. 1. In this group of 13 women over 50% had recurrence of disease within 2 yr of primary treatment.

Survival rates. The survival rates of patients with CEA levels ≤5, 5.1–9.9 and ≥10 ng/ml have been compared (Figs 2 and 3). Women with the highest pre-operative CEA levels had significantly less chance of survival over the time period studied than women with up to 5 ng/ml ($P < 0.005$; Fig. 2) or patients with CEA levels

Table 2. Distribution of CEA in normal women and patients with benign breast disease

		Total	≤2.5 ng/ml	2.6–5.0 ng/ml	5.1–9.9 ng/ml	≥10 ng/ml
Control	*n*	238	133	54	45	6
	%	100	56	23	19	3
Benign breast	*n*	65	39	15	8	3
disease	%	100	60	23	12	5

Table 3. Distribution of CEA according to stage and grade of disease: pre-surgical levels

		Total	≤2.5 ng/ml	2.6–5.0 ng/ml	5.1–9.9 ng/ml	≥10 ng/ml
All cases	*n*	628	327	150	110	41
	%	100	52	24	18	7
Stage 1	*n*	326	159	75	67	25
	%	100	49	23	21	8
Stage 2	*n*	266	152	66	34	14
	%	100	57	25	13	5
Grade 1	*n*	69	40	18	7	4
	%	100	58	26	10	6
Grade 2	*n*	255	135	64	42	14
	%	100	53	25	16	5
Grade 3	*n*	154	77	33	33	11
	%	100	50	21	21	7

Table 4. Distribution of CEA according to stage and grade of disease: post-surgical levels

		Total	≤2.5 ng/ml	2.6–5.0 ng/ml	5.1–9.9 ng/ml	≥10 ng/ml
All cases	*n*	577	320	146	84	27
	%	100	55	25	15	5
Stage 1	*n*	308	162	78	53	15
	%	100	53	25	17	5
Stage 2	*n*	249	150	62	26	11
	%	100	60	25	10	4
Grade 1	*n*	67	34	22	7	4
	%	100	51	33	10	6
Grade 2	*n*	236	138	56	34	8
	%	100	58	24	14	3
Grade 3	*n*	139	77	32	21	9
	%	100	55	23	15	6

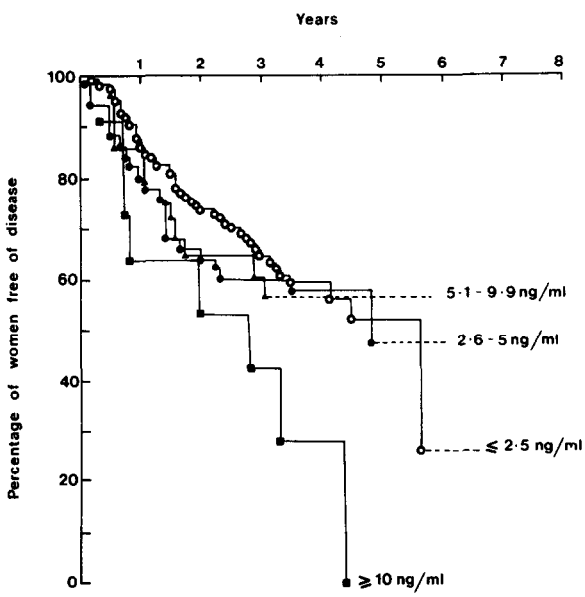

Fig. 1. Pre-operative CEA levels and recurrence rates in patients with stage II breast cancer. Recurrence curves are shown for patients with pre-operative CEA levels of: ≤2.5 ng/ml *(group A);* 2.6–5 ng/ml *(group B);* 5.1–9.9 ng/ml *(group C); and* ≥10 ng/ml *(group D). Group D was statistically different from group A* ($\chi^2 = 6.08$; $P < 0.025$) *but not group B* ($\chi^2 = 3.08$) *or group C* ($\chi^2 = 3.00$). *The number of women in groups A, B, C and D at time 0 was 127, 51, 29 and 11; year 1 was 111, 42, 24 and 7; year 2 was 90, 33, 18 and 6; year 3 was 55, 23, 15 and 3; year 4 was 26, 15, 7 and 1; year 5 was 7, 5, 2 was 0; and year 6 was 1, 1, 2 and 0 respectively. The number of women in this figure is not necessarily in accord with the numbers in the tables. This is because of patients being lost to follow up.*

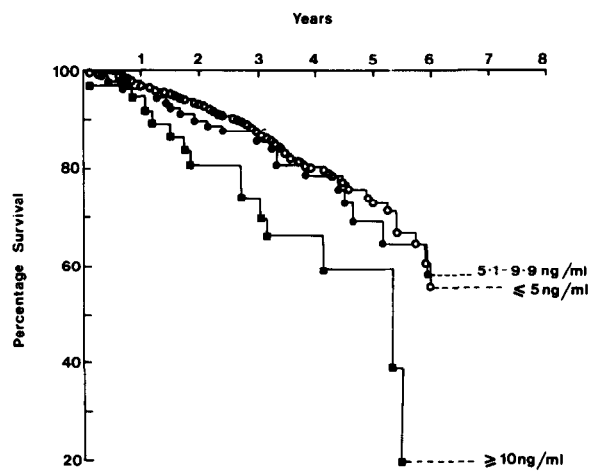

Fig. 2. Pre-operative CEA levels and survival rates. Survival curves are shown for all patients with pre-operative CEA levels of ≤5 ng/ml *(group A);* 5.1–9.9 ng/ml *(group B); and* ≥10 ng/ml *(group C). Both group A and group B were statistically different from group C* ($\chi^2 = 9.00$; $P < 0.005$ *and* $\chi^2 = 4.34$; $P < 0.05$ *respectively). The number of women in groups A, B and C at time 0 was 452, 96 and 38; year 1 was 440, 90 and 36; year 2 was 406, 80 and 29; year 3 was 284, 57 and 20; year 4 was 170, 36 and 10; year 5 was 64, 11 and 3; year 6 was 11, 6 and 1; and year 7 was 2, 0 and 0 respectively. The number of women in this figure is not necessarily in accord with the numbers in the table. This is because of patients being lost to follow up.*

between 5.1 and 9.9 ng/ml ($P < 0.05$). Although similar results were obtained using post-operative CEA levels, the differences did not reach formal statistical significance (Fig. 3).

Effect of mastectomy on serum CEA

The relation between changes in CEA levels 1 day before and 10 days after mastectomy and recurrence and survival rates was also examined. Mastectomy was not associated with any significant overall change in CEA levels, which is in accord with the distribution data in Tables 3 and 4. Of the 517 patients from whom pre- and post-

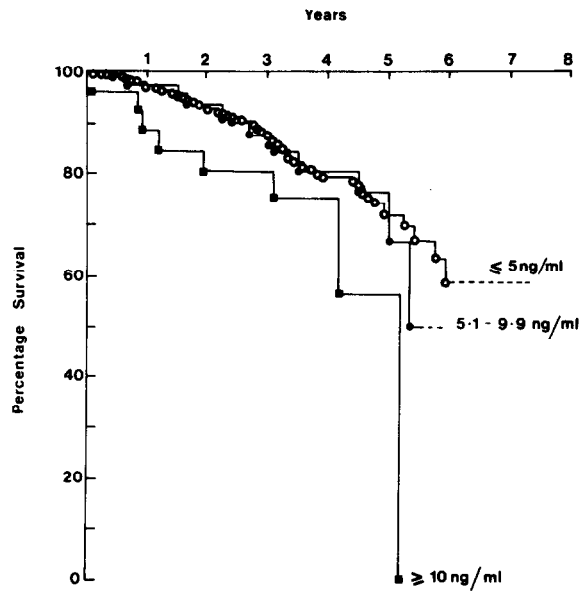

Fig. 3. Post-operative CEA levels and survival rates. Survival curves are shown for all patients with post-operative CEA levels of ≤5 ng/ml *(group A);* 5.1–9.9 ng/ml *(group B); and* ≥10 ng/ml *(group C). Group C was not statistically different from group A* ($\chi^2 = 3.80$) *or group B* ($\chi^2 = 2.60$). *The number of women in groups A, B and C at time* 0 *were* 437, 85 *and* 26; *year* 1 *was* 421, 81 *and* 23; *year* 2 *was* 386, 56 *and* 16; *year* 3 *was* 254, 56 *and* 16; *year* 4 *was* 133, 33 *and* 5; *year* 5 *was* 48, 8 *and* 1; *year* 6 *was* 8, 0 *and* 0; *and year* 7 *was* 2, 0 *and* 0 *respectively. The number of women in this figure is not necessarily in accord with the numbers in the tables. This is because of patients being lost to follow up.*

operative CEA assays were available, 263 showed an increase and 217 a decrease in serum CEA concentration 10 days after mastectomy; a further 37 exhibited no change. The clinical course and survival of patients in these 3 categories did not differ.

DISCUSSION

It is quite clear that, in our hands, the measurement of CEA is useless for diagnostic purposes. In this study the distribution of CEA in patients with benign breast disease or operable breast cancer, before or after treatment, is generally similar to that found in normal women. About 6% of cancer patients have values greater than 10 ng/ml compared to 3% in normal women. The normality of the distribution is in agreement with a previous publication from this laboratory [1]. Haagensen *et al.* [3] also reported that only 4% of patients undergoing mastectomy had CEA levels greater than the upper level for normal women. Doyle *et al.* [25] have reported that women with operable breast cancer have a distribution of CEA levels similar to that found in normal women.

In an earlier study we found 24% of patients before surgery had levels of CEA in excess of 5 ng/ml, and de Jong-Bakker *et al.* [19] give a value of 18%. Both these values are in accord with the present result of 25%. The population of control women in excess of 5 ng/ml in this and our previous report is 21 and 22% respectively. The results from the studies cited above are in contrast with those of Borthwick *et al.* [17], who found that 50% of patients with primary breast cancer had detectable levels of CEA, compared to 13% in normal women.

The amount of serum CEA is a poor index of prognosis and at best would apply to only 3–4% of patients whose CEA levels exceed 10 ng/ml before operation. Thus for the generality of women, the amount of CEA is not significantly related to the rapidity of recurrence of the disease. In terms of survival, pre-operative CEA levels in excess of 10 ng/ml were associated with a significantly increased rate of death, but the proportion of such women is only approximately 5%. Again, CEA measurements would be ineffective in predicting survival in the majority of patients. The levels of CEA are also inadequate in predicting stage or grade. Although a greater proportion of women with CEA in excess of 10 ng/ml was found in women with a grade 3 tumour, nevertheless 60% of such women had no detectable CEA at mastectomy. The failure of CEA to act as an adequate prognostic indicator has been commented on by de Jong-Bakker *et al.* [19], who have made the point that not all tumours produce CEA.

It has been suggested that frequent serial monitoring of CEA levels are of value as an early warning of recurrence, but de Jong-Bakker *et al.* [19] have reported a lead time of only 6 months. This is the best estimate and applies only to a minority of patients who show a consistent rise in CEA value with time. Others have found similar results [2, 3, 9, 18, 26]. None of these authors have produced any evidence that clinical benefit has resulted from using this information for the early introduction of therapy.

The results of the present study are in contrast with an earlier report from this laboratory [1] that CEA measured shortly after mastectomy was useful as an indicator of recurrence rates. The reason for this difference is unknown. It is unlikely to be observer bias since the earlier study was performed on coded plasma samples. A possible cause for the discrepancy is that the antibodies used in the radioimmunoassays in these two studies were cross-reacting with different CEA-related antigens [27–29].

This explanation is certainly consistent with an unpublished study in which we compared CEA measured by two other centres and ourselves on the same blood specimens. No correlation was

found between the results of the three centres. The comparison was based on approximately 700 specimens.

The antibody in this study was raised against CEA derived from a hepatic metastasis of a patient with colonic cancer, and therefore the question arises that this antibody may be inappropriate for the measurement of CEA in patients with breast cancer. This seems to be unlikely for the following reasons. Firstly, as has already been stated the proportion of women with early breast cancer with values of CEA greater than the upper level of normal (10 ng/ml) and in excess of 5 ng/ml are in agreement with the general literature. Secondly, de Jong-Bakker and colleagues [19], using the same antibody, found that in women with primary operable disease 42% had levels in excess of 5 ng/ml and that this percentage increased to 65% in women with advanced disease. Thirdly, these workers also found that changes in CEA levels reflected the clinical course of the disease. Thus, of 33 patients who were observed to have a clinical remission, 31 (94%) had decreases in their plasma CEA levels, whilst in 31 patients in which there was a progression of the disease, 20 (65%) were found to have an increase in their CEA levels. Finally, this study has shown that patients with early breast cancer who have levels of CEA in excess of 10 ng/ml in their blood have a significantly reduced survival time compared to women with CEA below this level.

It can be concluded that the determination of blood CEA is of no diagnostic value, but would identify 5% of women presenting with stage I or II disease who would have a high probability of a short disease-free interval and survival.

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