

Carcinoembryonic Antigen Levels in Cervico-vaginal Fluid from Patients with Intra-epithelial and Invasive Carcinoma of the Cervix*

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Abstract—Carcinoembryonic antigen (CEA) levels have been measured in cervico-vaginal washout fluid using the direct CEA Roche radioimmunoassay. Raised CEA levels were found associated with cervical intra-epithelial neoplasia and invasive carcinoma (85% above 300 ng/ml) compared with benign cervical lesions (29% above 300 ng/ml), suggesting that estimation of local CEA levels might be a useful adjunct to cytology and biopsy in the investigation of cervical neoplasia.

INTRODUCTION

INITIALLY thought to be specific for adenocarcinoma of the colon [1], raised serum carcinoembryonic antigen (CEA) has been found to be associated with non-neoplastic conditions and a variety of neoplasms [2-4].

Raised plasma CEA levels have been found in intra-epithelial and invasive squamous carcinoma of cervix [5, 6]. Since, however, the plasma level of CEA depends on the extent of the lesion [7], release of antigen and the activity of liver metabolism [8], it has been suggested that plasma CEA determination is of limited value for small, localised, invasive or intra-epithelial cervical carcinomas [7, 9].

The immuno-histological demonstration of CEA in both early invasive and intra-epithelial carcinoma [10] suggested that the study of CEA levels in local cervical secretions might be a useful adjunct to exfoliative cytology and tissue biopsy in the study of cervical epithelial neoplasia.

MATERIALS AND METHODS

Cervico-vaginal fluid

Cervico-vaginal fluid was obtained by the instillation into, and retrieval from, the vagina of

8 ml of phosphate-buffered saline (PBS), pH 7.4, so that the fluid washed over the cervix. Fluid from 136 patients who were undergoing diagnostic biopsy was available for analysis: of these patients, 66 had intra-epithelial or invasive carcinoma and 70 had lesions considered benign.

The CEA content in the retrieved fluid was measured by the direct CEA Roche radioimmunoassay test.

Cervical biopsies

The cervical biopsies were fixed in formal saline, routinely processed, paraffin-embedded and sectioned at 3 μ m. Haematoxylin and eosin-stained sections were examined for the histological diagnoses, under the following headings: chronic cervicitis, mild dysplasia, moderate dysplasia, severe dysplasia, *in situ* carcinoma and invasive carcinoma. Mild and moderate dysplasia with chronic cervicitis formed the group considered benign. The malignant and premalignant group was constituted by invasive carcinoma, *in situ* carcinoma and severe dysplasia.

Analysis

The levels of CEA in the washout fluid from the malignant and non-malignant groups were compared. A second comparison of the CEA levels of all six histological subgroups was made. Statistical analysis was by Student's *t* tests.

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RESULTS

Analysis of the CEA level in the washout fluid in the benign group showed a mean value of 267 ng/ml, with a range of 10–975 ng/ml. Seventy-one were below 300 ng/ml.

In the group with lesions considered to be malignant or pre-malignant, the CEA levels ranged from 22 to 2150 ng/ml, with a mean of 694 ng/ml. Eighty-five percent were above 300 ng/ml.

When the benign lesions—chronic cervicitis and mild and moderate dysplasia—were compared, the distribution of CEA in the different histopathological subgroups (Fig. 1) showed little difference in range or mean level, apart from isolated high levels. The 36 cases of chronic cervicitis had a range of 10–816 ng/ml, with a mean level of 266 ng/ml; 69.4% of the levels were below 300 ng/ml. In mild dysplasia (17 cases) the range was 73–975 ng/ml, the mean was 283 ng/ml, and 70% of cases were below 300 ng/ml. Moderate dysplasia (17 cases) had a range of 71–437 ng/ml and a mean of 253 ng/ml, with 73% below 300 ng/ml.

Severe dysplasia and *in situ* carcinoma had markedly higher mean values (551 and 683 ng/ml respectively) than any of the benign group, but were not significantly different from each other ($P > 0.1$). The 19 cases of severe dysplasia ranged from 22 to 950 ng/ml, while the 34 cases of *in situ* carcinoma ranged from 42 to 2150 ng/ml. Seventy-nine percent of the severe dysplasia cases and 85.3% of the *in situ* carcinomas were above 300 ng/ml.

Invasive carcinoma (13 cases) had the highest mean level, 933 ng/ml of all the groups, with only 1 case (8%) below 300 ng/ml and a range of 159–2000 ng/ml.

DISCUSSION

In the investigation of plasma CEA values in relation to carcinoma of the cervix, raised levels have been found in some cases of both intra-epithelial and invasive carcinoma [5, 6]. Since,

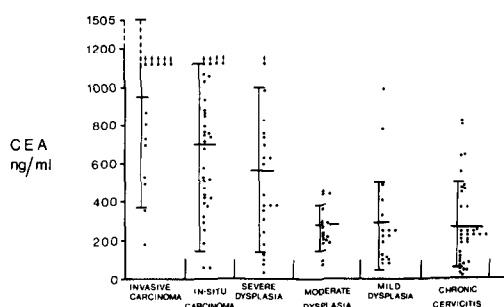


FIG. 1. Cervico-vaginal washout CEA levels in the 6 histological subgroups: chronic cervicitis, mild dysplasia, moderate dysplasia, severe dysplasia, *in situ* carcinoma and invasive carcinoma. —Indicates the mean level \pm standard deviation.

however, the plasma level of CEA depends on various factors, including the extent of the lesion [7] and the rate of liver metabolism [8], plasma assay has been found to be of limited value [7, 9]. In view of this, it was felt that in the study of CEA in early malignancy of pre-malignant lesions, the measurement of CEA in local fluids might provide a better association with neoplastic transformation than the measurement of circulating CEA, as has been shown in urothelial carcinoma [11].

The results of the present series show that the CEA level in cervico-vaginal washout fluid from patients with no evidence of malignancy, or definite pre-malignancy, is below 300 ng/ml in 71% of the cases, providing a marked distinction with the pre-malignant epithelial lesions and invasive carcinoma—in which only 15% had levels less than 300 ng/ml. Statistical comparison of the mean levels of the benign and pre-malignant/malignant group showed a significant difference ($P < 0.001$). In intra-epithelial neoplasia—*in situ* carcinoma and severe dysplasia—83% had CEA levels over 300 ng/ml. Again, the mean level was significantly higher ($P < 0.01$) than the mean value of any of the benign groups.

These figures suggest the presence of CEA or CEA-like antigen in secretions associated with both benign and pre-malignant or malignant cervical epithelial lesions, but the levels associated with pre-malignant or malignant changes are much higher than those found with benign lesions. In contrast to plasma estimation, high levels are frequently found associated with intra-epithelial malignancy.

The raised values found without histologically proven epithelial malignancy might be due to punch biopsies missing the appropriate area, or to some mild or moderate dysplastic lesions being pre-malignant and producing CEA before they have developed the morphological features of severe dysplasia or *in situ* carcinoma.

The low CEA values found associated with definite intra-epithelial or invasive carcinoma may be explained by the fact that some cervical carcinomas, estimated at 15% [6], either do not produce CEA or produce extremely small amounts. Our figure of 15% of patients with histological epithelial malignancy and low levels of CEA is in agreement with this.

With the increasing use of colposcopy in the investigation of abnormal cervical smears, it is suggested that the estimation of CEA in local cervical secretions might provide a useful objective adjunct to the subjective interpretation of colposcopy, cytology and biopsy histopathology.

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