Eur J Cancer Clin Oncol. Vol. 20, No. 3, pp. 369–374, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Cumulative Effects of Age and Pathology on Plasma Carcinoembryonic Antigen in an Unselected Elderly Population

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Abstract—*Plasma CEA was measured in 776 institutionalized elderly patients, 593 women and 183 men, whose mean age was 80.8 ± 9.7 yr. Of these subjects 39 were found to be free of any pathology and were considered as a control group. All the other subjects had a variety of diseases, malignant or not, known or not known to be associated with elevated CEA. This study showed that elderly people in their 80s, in apparent good health, had higher levels of CEA (3.0 ± 1.4 ng/ml) than younger people. These levels were shown to be significantly increased in a large number of non-malignant diseases. No correlation could be found between elevated CEA values and autopsy finding or drug administration. Using the chi square test, the number of patients with CEA levels greater than 5 ng/ml was found to be significantly higher in chronic renal failure and cancer. Mortality was also found to be higher in patients with CEA levels greater than 5 ng/ml during a 25-month follow-up. Higher levels of CEA in elderly subjects in apparent good health, as well as increase of these levels in a large set of non-malignant pathology, must thus be kept in mind when interpreting data arising from old people because of both the false-positive (healthy elderly subjects) and the cumulative effects of polypathology on plasma CEA.*

INTRODUCTION

ALTHOUGH it is clear that age should always be considered when interpreting biological data, the question is still debated whether aging itself may be solely responsible for abnormal biological values. The occurrence of pathological conditions increases considerably with age and may also account for such abnormalities. In this respect, carcinoembryonic antigen (CEA) plasma levels should be considered with particular attention in the elderly since elevated values have been found to be associated with a wide variety of both malignant and non-malignant diseases [1–3]. Although some studies attempted to look for the effects of age upon CEA plasma levels, it still remains unclear whether elderly people have different reference values or whether the polypathology of the elderly increase the levels of plasma CEA [4–6]. In such a case, CEA assay could well result in a misinterpretation when performed in the aged population.

This study was designed to document and analyse the cumulative effects of age and pathology on CEA plasma levels in an institutionalized elderly population, taking into account medical history, biological data and autopsy findings.

MATERIALS AND METHODS

Plasma CEA assays were performed over a 7-month period in 776 unselected, institutionalized elderly subjects (593 women and 183 men) whose mean age (± S.D.) was 80.8 ± 9.7 yr (men = 74.9 ± 10.2; women = 82.3 ± 8.7 yr). About 78% of the patients were over 75 yr old, and most of them were women (Table 1).

The patients were hospitalized in long-term

Accepted 5 September 1983.
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care units for a variety of diseases requiring constant medical assistance and could not therefore be regarded as representative of a normal, healthy elderly population. All of them possessed documented medical records whose relevant data were processed by a computer for the purpose of this study. Each questionnaire included informations such as age, sex, smoking and/or alcoholic habits, liver and biliary diseases (cirrhosis, biliary obstruction, viral hepatitis), respiratory diseases (bronchitis, asthma, emphysema, tuberculosis, exposure to pulmonary toxins), neurologic diseases (cerebral stroke, senile dementia, lacunar syndrome, Parkinson's disease), gastro-intestinal diseases (ulcus, colitis, diverticulitis, polyposis, chronic diarrhoea), bone and joint diseases (arthritis, Paget's disease, gout or pseudo-gout), cardiovascular diseases (myocardial infarction, severe angina pectoris, cardio-pulmonary failure), inflammatory syndrome (hyper α_2-globulinemia and sedimentation rate $\geqslant$80 mm), hypertension, diabetes, chronic renal failure and malignant pathology.

Of the subjects, 39 (9 men and 30 women; 5% of the population) were found to be free of any pathology and/or alcoholic and smoking habits at the time of the study. They could therefore be considered as a control group whose mean age ± S.D. was 84.0 ± 8.0 yr.

Venous blood samples were drawn under standardized conditions (08.00–09.30 hr) and were immediately centrifuged. Each plasma aliquot was stored frozen at -20°C until assayed. A solid-phase enzyme immunoassay based on the sandwich principle was used (Abbott kits). The results obtained with this method were comparable to those obtained with radioimmunoassays: coefficient of correlation = 0.95, $P < 0.001$; sensitivity level: 0.25 ng/ml [7]. The statistical significance of the relation between the different pathological conditions and the elevated CEA plasma levels was assessed by the chi square test. Student's t test was used for comparison of the means.

Forty patients with CEA values greater than 5 ng/ml in relation with non-malignant diseases were assayed for CEA plasma levels every other month over a period of 6 months ($n = 4$ samples). An analysis of variance was performed in order to evaluate the time-dependent intra-individual variation in such non-malignant diseases and thus to estimate the reliability of CEA measurements.

During the 25 months follow-up of this study 268 patients died (34.5%). A complete autopsy was performed in 240 of them. The relation between significant autopsy findings (occult chronic disease, undiagnosed neoplasms, etc.) and CEA plasma levels was assessed by the chi square test.

RESULTS

Plasma mean levels

The mean levels (± S.D.) of the 776 elderly patients of the study was 4.0 ± 8.1 ng/ml; however, three patient with malignancies had particularly elevated plasma CEA levels (up to 160 ng/ml). Because of the major interference of these extremely high values on both the general mean and standard deviation, they have not been taken into account for the rest of the study. The mean level of plasma CEA of the 773 other patients was therefore 3.5 ± 2.1 ng/ml (Table 1). One hundred and twenty-two subjects (15.7%) showed a CEA value of 5 ng/ml or greater and among them 15 (1.9%) had values of 10 ng/ml or greater (Table 1). The healthy control group (39 subjects) had CEA values of 3.0 ± 1.4 ng/ml (Table 2).

Sex

No significant difference attributable to sex could be observed in elderly subjects (Table 1).

Table 1. Distribution and mean levels (ng/ml) of plasma CEA in 773 patients: age and sex-related effects

		Patients No.	Patients %	% of patients as a function of CEA level <2.5	⩾2.5 <5	⩾5 <10	⩾10	Mean level ± S.D.
Age (yr)	<65	48	6.2	52.1	43.7	4.2	—	2.8 ± 1.5*
	65–74	126	16.3	33.3	51.6	13.5	1.6	3.6 ± 2.6
	75–84	313	40.5	35.8	47.6	16.0	0.6	3.4 ± 1.8
	⩾85	286	37.0	22.1	61.9	13.1	2.8	3.8 ± 2.3
All subjects		773	—	35.7	48.6	13.8	1.9	3.5 ± 2.1
Sex	Men	183	23.7	47.0	41.0	10.5	1.5	3.3 ± 2.3
	Women	590	76.3	32.2	51.0	14.8	2.0	3.6 ± 2.1

*Patients who were under 65 yr had statistically lower ($P < 0.02$–0.001) levels of CEA than any other age-groups.

Table 2. Distribution and mean levels (ng/ml) *of plasma CEA in 773 unselected elderly patients: effects of pathology*

Pathology	No. of patients	% of patients as a function of CEA level <2.5	⩾2.5 <5	⩾5	Mean levels ± S.D.
None	39	41.0	46.1	12.8	3.0 ± 1.4
Cancer					
No	680	36.0	48.8	15.3	3.5 ± 2.5
Past	49	26.5	53.1	20.4	3.6 ± 1.8
Evolutive	47	46.8	25.5	27.7	10.5 ± 31.1
Renal failure					
No	665	37.3	48.1	14.6	3.4 ± 2.0
Yes	108	25.9	51.9	22.2	4.1 ± 2.7*†
Inflammatory syndrome					
No	652	37.3	48.0	14.6	3.4 ± 2.0
Yes	121	27.0	51.6	21.3	4.0 ± 2.6*†
Respiratory diseases					
No	597	35.6	49.1	15.4	3.5 ± 2.0
Yes	174	36.2	46.9	16.9	3.7 ± 2.6*
Gastro-intestinal diseases					
No	667	36.3	48.5	15.2	3.5 ± 2.2
Yes	106	32.1	49.0	18.9	3.7 ± 2.0*
Liver and biliary diseases					
No	654	35.9	49.3	14.8	3.5 ± 2.1
Yes	119	34.7	44.6	20.6	3.8 ± 2.2*
Bone and joint diseases					
No	646	36.7	48.4	14.9	3.5 ± 2.1
Yes	127	30.7	49.6	19.7	3.8 ± 2.2*
Heart diseases					
No	613	35.8	48.6	15.6	3.5 ± 2.2
Yes	159	35.0	48.7	16.3	3.6 ± 2.1*
Hypertension					
No	576	35.6	49.7	14.7	3.4 ± 1.9
Yes	196	35.7	45.4	18.9	3.8 ± 2.6*
Neurologic diseases					
No	386	34.4	47.0	18.5	3.7 ± 2.3
Yes	387	37.0	50.1	12.9	3.4 ± 2.0
Diabetes					
No	694	35.8	48.0	16.2	3.6 ± 2.2
Yes	79	35.0	53.8	11.2	3.3 ± 1.5
Smokers					
No	584	33.8	50.5	15.7	3.5 ± 1.9
Former	100	40.0	44.0	16.0	3.8 ± 3.3
Current	84	43.5	40.0	16.5	3.4 ± 1.9
Alcoholics					
No	632	34.7	49.4	15.6	3.5 ± 2.0
Former	89	41.6	44.9	13.5	3.3 ± 1.9
Current	50	39.2	43.1	17.6	4.0 ± 3.5

*Plasma mean levels of CEA significantly ($P < 0.05$–0.01) larger in the presence (yes) of the pathology when compared to the control group of healthy elderly subjects ($n = 39$).

†Plasma mean levels of CEA significantly ($P < 0.02$) larger in the presence (yes) than in the absence (no) of the specified pathology.

CEA levels in different age-groups

Patients over 65 yr had significantly higher plasma levels of CEA than patients under 65 yr (Table 1). The number of subjects with CEA values greater than 5 ng/ml was also found significantly higher using the chi square test for the same age range ($\chi^2 = 5.15$, $P < 0.05$).

Alcohol and cigarette smoking

Eighty-four patients (10.9%) were considered as heavy smokers (0.5–2 packs a day for more than 10 yr) and 50 (6.5%) were known as chronic alcoholic abusers. Their plasma CEA level were 3.4 ± 1.9 and 4.0 ± 3.5 ng/ml respectively and did not appear different from that found in the non-smoker and non-drinker populations (Table 2). The chi square test also failed to demonstrate any relation between CEA values greater than 5 ng/ml and smoking or alcohol addition.

Cancer

Ninety-six patients (12.4%) had a cancer either clinically diagnosed ($n = 81$) or found at autopsy ($n = 15$). Among them, 23 had CEA levels of 5 ng/ml or higher. Although the mean levels in patients suffering from an evolutive cancer was high, the difference with both the non-cancerous patients and the healthy control group was not significant, due to large standard deviations (Table 2). However, the number of subjects with CEA values greater than 5 ng/ml was found to be significantly higher ($\chi^2 = 8.14$, $P < 0.01$) in the presence than in the absence of an evolutive cancer using the chi square test.

Table 3 shows the mean levels of plasma CEA according to the localization of cancer. CEA levels were high with large standard deviation in 3 occurrences, i.e. cancer of colon and of the bladder and in patients with metastases of non-proven origin.

Table 3. Mean plasma levels of CEA (ng/ml) *in 96 patients with malignant diseases*

Cancer localization	Patients No.	%	Mean levels ± S.D.
Skin	22	22.9	4.1 ± 2.1
Breast	16	16.7	4.2 ± 3.1
Colon	12	12.5	28.1 ± 59.4
Rectum	7	7.3	3.3 ± 1.3
Bladder	6	6.3	5.0 ± 4.7
Hematopoietic organs	5	5.2	2.5 ± 1.2
Metastases of non-proven origin	4	4.2	8.4 ± 10.3
Liver	3	3.1	3.8 ± 1.7
Stomach	3	3.1	2.7 ± 1.6
Uterus	3	3.1	2.1 ± 0.7
Ovary	3	3.1	4.2 ± 3.3
Prostate	2	2.1	4.1 ± 3.3
Kidney	1	1.0	2.1
Upper respiratory tract	1	1.0	2.0
Other	8	8.3	3.9 ± 1.8

Other pathology and autopsy findings

Mean plasma levels of CEA were not significantly different in patients with a determined pathology when compared to all the other patients free of this specified pathology, except in patients with chronic renal failure and inflammatory syndrome (Table 2). The chi square test also demonstrated a relation between chronic renal failure and CEA values greater than 5 ng/ml ($\chi^2 = 4.00$, $P < 0.05$), but failed to demonstrate any relation in all other studied pathologies.

When compared to the control group of healthy subjects ($n = 39$) the levels of CEA were found to be significantly higher in a large number of pathologies (Table 2). No relation could be found between abnormal CEA plasma levels and either autopsy findings (Table 4) or drug administration. The analysis of variance (40 non-malignant patients with elevated CEA levels were sampled once every other month over a 6-month period) showed that if, indeed, the variability between individuals was large, the time-related intra-individual variability was non-significant (Table 4) for those patients with high CEA values not related to malignant diseases.

Table 4. Mean plasma levels (ng/ml) *of CEA related to autopsy findings in 240 deceased patients*

Autopsy findings	Patients No.	%	Mean levels ± S.D.
Gallbladder lithiasis	73	30.4	3.9 ± 2.9
Biliary obstruction	23	9.6	3.8 ± 2.0
Liver steatosis	22	9.2	3.0 ± 1.6
Diverticulitis	22	9.2	4.4 ± 2.9
Chronic pancreatitis	18	7.5	3.4 ± 1.5
Liver fibrosis	17	7.1	3.2 ± 1.6
Uterine fibroma	14	5.8	3.6 ± 1.1
Liver cirrhosis	12	5.0	3.7 ± 1.3
Ovarian cyst	10	4.2	3.1 ± 1.1
Kidney lithiasis	9	3.8	3.2 ± 1.1
Various non-malignant tumors	20	8.3	3.4 ± 1.7

Mortality

Of the 268 patients who died during the 25-month follow-up period a significantly higher number of patients with CEA plasma levels greater than 5 ng/ml was found (among the deceased population) using the chi square test ($\chi^2 = 4.18$, $P < 0.05$).

DISCUSSION

Several reports dealing with presumably healthy subjects have pointed out that about 5–15% of them have CEA plasma levels higher

than 2.5 ng/ml and 1–3% have values higher than 5 ng/ml [2, 3, 8–10]. The present study shows that elderly subjects in their 80s are far more likely to have a positive CEA test than younger subjects: 64.3% of the population had CEA levels higher than 2.5 ng/ml; among them a large percentage of the elderly had CEA levels higher than 5 ng/ml, i.e. 15.7% when considering the population as a whole and 12.7% when considering the control group of 39 elderly healthy subjects. As a consequence of this distribution, the levels of CEA in the plasma of elderly subjects were found to be larger (3.5 ± 2.1 ng/ml, $n = 773$), even in subjects without any known disease (3.0 ± 1.4 ng/ml, $n = 39$), when compared with data in the literature dealing with younger populations [8, 10, 11]. The question must be raised of whether elevated CEA levels in elderly subjects is related to age itself or to the well-known polypathology, malignant or not, of the aged [12]. Our data strongly suggest that elderly subjects in apparent good health have higher levels of plasma CEA than younger subjects. Besides, elderly folk over 65 yr had higher CEA levels than subjects under this age, without any sex-related difference. This is important to emphasize as previously published reports on CEA and aging did not look for CEA levels on subjects above 60 yr. Indeed, these latter subjects, if any, were integrated into large age-groups, e.g. over 50 yr [6, 8, 10, 11]. Besides, no data are to be found with respect to healthy elderly people over 65 yr. This paper is, to our knowledge, the only one that investigates and compares CEA levels in a large number of elderly folk over 65 yr either healthy or suffering from benign or malignant conditions. Plasma levels of CEA were also shown to be significantly increased (up to 4.1 ng/ml) in non-malignant diseases when compared to the healthy control group. It is to be noted that, whatever the non-malignant pathology, CEA levels were never higher than 4.1 ng/ml, a fact which is worth underlining when taking into account the polypathology of this elderly population. Elevated CEA levels could not be related to the administration of drugs since no effect of treatment (mostly polymedication) could be observed on CEA values. In addition, no correlation could be found, using the chi square test, between CEA levels and autopsy findings. However, mortality was found to be significantly higher in patients with CEA levels greater than 5 ng/ml during the 25-month follow-up. The chi square test also demonstrated a relation between chronic renal failure and elevated CEA levels.

The variability between individuals was large, whereas the time-related intra-individual variability was not significant for high CEA values not related to a malignant disease.

Of the 96 patients with a malignant disease 47 had an evolutive cancer, and the number of patients with elevated CEA levels was found to be significantly higher in this case. Elevated CEA levels were found in cancer of the colon and bladder and in patients with metastases. It is to be noted that 15 cancers not clinically detected were found at autopsy: CEA levels in these patients were elevated in 7 cases. These data, together with those of Stevens *et al.* [5], allow us to consider that elevated CEA in presumably non-cancerous elderly patients may be considered as a risk for the development of a cancer. In conclusion, our data showed that elderly subjects in apparent good health had elevated CEA levels, with a large inter-individual variability. These levels were even more increased in a large set of both non-malignant and malignant diseases. These results should thus be kept in mind when interpreting data arising from old people since the follow-up of CEA in the elderly suffering from a malignant disease could be a matter of controversy because of the false-positive (healthy subjects over 65 yr) and the cumulative effects of a large set of diseases, malignant or not, upon the levels of plasma CEA.

Acknowledgement—We wish to thank Abbot Labs for their help in this study.

Table 5. Analysis of variance: effect of time on CEA plasma levels in 40 patients with non-malignant elevated (≥5 ng/ml) CEA

Variability tested	Sum of squares	Degrees of freedom	Estimate of variance σ^2	F	P
Inter-individual variability	1213.7	38	31.9	17.7	<0.001
Time-related intra-individual variability	12.7	3	4.2	2.3	N.S.

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