Prevalence of Abnormal Levels of Serum Tumour Markers in Elderly People

Luis A. Lopez, Valentín Del Villar, Mariano Ulla, Francisco Fernández, Luis A. Fernández, Idelfonso Santos, Luis Rabadán, Martín Gutierrez

Summary
The study was conducted to evaluate the prevalence of abnormal levels of several serum tumour markers in an institutionalized elderly population.

Serum tumour markers assay of carcinoembryonic antigen (CEA), the carbohydrate antigens CA 19-9, CA 72-4 and CA 15-3 (Enzymun-test, Boehringer Mannheim GmbH Diagnostic), alpha-fetoprotein (AFP) and prostate specific antigen (PSA) (Abbot Diagnostic Division) were performed in 228 unselected, institutionalized elderly subjects, whose mean age (SD) was 82.4 (5.79) range (66—99 years). Patients with acute or neoplastic diseases were excluded from the study. The serum markers were also measured in 52 healthy young adults (controls).

Using the established threshold values, 92 subjects (40%) were found to have at least one elevated marker. PSA was elevated in 33%, CA 19-9 in 16%, CEA in 11.5%, CA 15-3 in 11%, CA 72-4 in 8% and AFP in 3%. We found a significant difference in the serum levels between the two groups for CEA, CA 19-9, CA 15-3, and PSA (p < 0.001).

Healthy aged people appear to have an elevated prevalence of elevated levels of serum tumour markers. The results suggest that apart from PSA, elevated antigen levels in elderly subjects are related to the ageing process itself rather than to occult pathology.

Introduction
The ageing of the population in industrialized countries is a well known and widely studied phenomenon [1, 2]. In Spain, 13.7% of the population are over 65 years old [3]. Soria takes fifth place amongst the Spanish provinces with the greatest number of elderly inhabitants, with 21.9%. The incidence of the commonest human tumours increases with age [4, 5]. Studies of the incidence of tumours in the USA collected through the SEER Program [6] show that 55% of all tumours occur in elderly people, the incidence of cancer rising from 300 per 100 000 persons per year in the 45-49-years’ segment, to 2500 at 80-84 years.

The search for tumour markers which would be effective in screening high-risk subjects is an active area of cancer research [7]. Although certain technical factors are important in assessing a marker, the most important is the prevalence of the disease in the population under study [8, 9]. The incidence of tumours in the elderly population is high [6, 10-12], and older people are motivated to participate in health programmes [13]. When interpreting laboratory data it is important to know the effect of age to make a correct assessment of the results, but it has not been established whether ageing alone is responsible for the changes found in certain biological indices, or whether such abnormalities are attributable to pathological or degenerative conditions that have a high prevalence in the elderly population [14].

The purpose of this study was to measure the prevalence of abnormal levels of some of the serological tumour markers in a sample of elderly people. We have selected a panel of tumour-associated antigens that includes the following markers: carcinoembryonic antigen (CEA), prostate specific antigen (PSA), alpha-fetoprotein (AFP), the carbohydrate antigens CA 19-9, CA 15-3, and CA 72-4, and ferritin.

Methods
We studied elderly people living in two nursing homes for the elderly in Soria, Spain. Subjects with a prior or current neoplastic disease or the presence of a serious disease of any other aetiology were excluded from the study. From the original population of 238 subjects, 10 were excluded for different reasons: three were absent when the samples were drawn; four had cancer; one showed multi-systemic organic impairment and two refused to co-operate in the study. This left 228 cases with a mean age of 82.4 (SD 5.79) years (range 66—99). There were 81 men (35.5%) and 147 women (64.5%).
In four cases there was liver disease (1.75%) and in 31 (13.5%), kidney failure, with serum creatinine levels of over 1.2 mg/dl, reaching figures of 2 mg/dl or more in three cases only. Thirteen (5.7%) of the 228 subjects were smokers. The prevalence of anaemia was low in the study sample at 3.5%. None had required hospitalization during at least 6 months before the samples were collected. The frequency distribution of the ages of the tested sample is shown in Table I. We excluded from the statistical summary one subject in whom a carcinoma was diagnosed shortly after the sample collection; the tumour markers furnished exceptionally high figures of CA 19-9 and CEA. By the time the data were processed (June 1994) 28 (12.2%) of the 228 original subjects had died, eight of them from neoplastic diseases.

The control group was selected from students at the Soria nursing college and health staff from the INSALUD hospital. They amounted to a total of 52 subjects with a mean age of 23.1 (SD 4.1) years (range 18–35). There were 15 men (28.8%) and 37 women (71.2%). The 228 subjects in the study and the 52 controls were volunteers and gave their informed written consent.

Blood samples were drawn between February 1991 and August 1992, three tubes being extracted: one with EDTA for a lymphocyte and complete blood count, and two for serum. Once in the laboratory, the EDTA sample was processed immediately and the tubes with clotted blood were centrifuged, divided into aliquots and the ferritin measured, while the rest was frozen at —30°C for subsequent measurement of tumour markers. Blood counts were made using the Sysmex N-8000 auto-analyser (Toa diagnostic division). For samples in which the device failed to identify the differential count properly, a manual count was made.

Measurement of tumour-associated antigens: We divided the serum measurements into two groups, following the methods or assays used: IMX system (Abbott diagnostic division), a commercial microparticle enzymatic immunological assay used for measuring ferritin and PSA; and Enzymum-test (Boehringer Mannheim GmbH diagnostic division), a commercial immunoenzyme assay for CEA, CA 72-4, CA 15-3, AFP, and CA 19-9. Established cut-off points were: 4 ng/ml for PSA, 5 ng/ml for CEA, 6.7 IU/ml for CA 72-4, 30 IU/ml for CA 15-3, 7 IU/ml for AFP, and 37 IU/ml for CA 19-9.

Statistical methods: We measured the mean as centralization measure, the variance and the standard deviation (SD) as dispersion indices, and the minimum and maximum values for indicating the range of all the quantitative variables. The standard error of the mean (SEM), was measured as a parameter for estimating a population from the sample. The goodness of fit of the quantitative variables to a normal distribution was estimated using the Kolmogorov–Smirnov test, the hypothesis of normality being rejected when there was a probability of under 0.05. The comparison of two quantitative variables was made by the Mann–Whitney U test for non-parametric variables and by the Student's t test for parametric. The Pearson coefficient was used for correlating variables. The statistics were processed with a statistical program for IBM, STATGRAPHICS (Statistical graphics corporation, 1991 STSC Inc.).

Results

We found elevated markers in 92 (40.35%) elderly subjects. Two markers were high in 20 subjects (8.7%), three in 7 (3.07%) and four in two (0.87%). The most prevalent antigen was PSA, which was found to be above the established cut-off point in 33.3% of the men. The rest of the markers were measured in both sexes; the percentages of subjects above the cut-off are shown in Table II. In the 52 control subjects there were increased values of one marker, the CA 72.4, in three subjects (5.6%). The descriptive statistics of the cases and controls are shown in Tables III and IV. In general, increases in the markers were moderate, although 3.5% of the elderly subjects had CA 19-9 values of over 75 IU/ml, and 7.7% of men had PSA values over 20 ng/ml. The comparison of the means for the different variables measured and the level of statistical significance comparing the control group with the study population are shown in Table V. We compared men and women for all the variables in the group of cases and found statistically significant differences only in ferritin (p = 0.002, Mann–Whitney U test). Since kidney failure changes the levels of some markers [15, 16], we have compared the subjects of the series showing some degree of kidney failure with the rest and have found no significant differences in any of the markers. The majority of patients showing evidence of renal impairment has only minimally elevated creatinine levels.

We found no significant relationship between the tumour markers and the lymphocyte count. We also found no relationship between the tumour-associated antigens and serum ferritin values. A correlation was found between the lymphocyte count and age (r = 0.35;
Table III. Study group: descriptive statistics

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean</th>
<th>Variable</th>
<th>SD</th>
<th>SEM</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>226</td>
<td>2.85</td>
<td>5.12</td>
<td>2.26</td>
<td>0.15</td>
<td>0.1</td>
<td>20.6</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>226</td>
<td>21.47</td>
<td>493.3</td>
<td>22.21</td>
<td>1.48</td>
<td>2.3</td>
<td>151.8</td>
</tr>
<tr>
<td>PSA</td>
<td>78</td>
<td>7.58</td>
<td>210.2</td>
<td>14.5</td>
<td>1.64</td>
<td>0.1</td>
<td>73.3</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>227</td>
<td>18.05</td>
<td>86.35</td>
<td>9.29</td>
<td>0.62</td>
<td>3</td>
<td>81.9</td>
</tr>
<tr>
<td>CA 72-4</td>
<td>227</td>
<td>3.51</td>
<td>10.84</td>
<td>3.29</td>
<td>0.22</td>
<td>2</td>
<td>25.2</td>
</tr>
<tr>
<td>AFP</td>
<td>227</td>
<td>3.07</td>
<td>2.41</td>
<td>1.55</td>
<td>0.10</td>
<td>0.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Ferritin</td>
<td>227</td>
<td>133.96</td>
<td>16.219</td>
<td>127.35</td>
<td>8.43</td>
<td>3</td>
<td>762</td>
</tr>
</tbody>
</table>

p = 0.003), between some carbohydrate antigens, and between age and several markers (data not shown).

Discussion

We have found no study in the literature reporting the prevalence of tumour markers in asymptomatic subjects aged 75 years or more. There is some information on the association of age with serum levels for each antigen, but it is sometimes conflicting, and is generally restricted to a single marker.

A trend for older people to have CEA values higher than the rest of the population has been suggested, which cannot apparently be explained by a greater prevalence of non-neoplastic diseases [17, 18]. Stevens et al. [19] measured the CEA in 956 elderly patients, taking a value of 5 ng/ml as a reference; 4.5% of the sample, showed equal or higher values. Most of the subjects included in the study were aged 60–69 (62.4%), and only 7.6% were over 80 years old. Touitou et al. [20] analysed the association of age and of specific pathological conditions with serum levels of CEA, studying an elderly institutionalized sample. Seventy-eight per cent of the subjects studied were over 75 years old; 15.7% showed values above the cut-off point.

As far as CA 19-9 is concerned, Del Vilano et al. [21] established reference values in a long series of non-selected controls chosen from 1020 regular blood donors. The authors found statistically significant differences with age in women only, with the highest values in the 20- to 29-year-old group; the lowest values were found in the oldest women studied (60–69 years).

Little is known about the changes in CA 15-3 with age. In a series of 1050 female blood donors no association of antigen levels with age was reported [22].

We have only found one work analysing the association of age with CA 72-4 antigen levels [23]. Again, the population consisted of blood donors and did not include people aged over 65 years. The authors showed a significant decrease in serum levels with age in both sexes.

There is some discrepancy as to whether alpha-fetoprotein levels change with age; some authors have found differences [24, 25] while others have not [26]. A third group noted differences with age, with AFP levels increasing to reach a plateau stage at 50–60 years [27].

The prostate specific antigen does vary with age. Brawer et al. [28] studied a population of more than 1200 men with a mean age of 66.8 years, only 5% of the sample being over 79, and found that the marker levels increased with age. Babaian and co-workers [29] estimated the prostatic volume and measured the PSA in 492 subjects with no clinical evidence of prostatic cancer, or with negative biopsies; the mean age of the group studied was 62 years (29–84), with only 17% of the subjects being older than 70 years. They showed an association between the PSA level and age, and between the age of the patient and the volume of the prostate gland.

We have measured a series of tumour-associated antigens in a very elderly sample, finding a high prevalence of practically all the markers studied.

Table IV. Control group: descriptive statistics

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean</th>
<th>Variable</th>
<th>SD</th>
<th>SEM</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>52</td>
<td>1.31</td>
<td>0.42</td>
<td>0.65</td>
<td>0.09</td>
<td>0.3</td>
<td>3.3</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>52</td>
<td>6.61</td>
<td>19.18</td>
<td>4.38</td>
<td>0.61</td>
<td>2.2</td>
<td>21.1</td>
</tr>
<tr>
<td>PSA</td>
<td>15</td>
<td>0.69</td>
<td>0.19</td>
<td>0.43</td>
<td>0.11</td>
<td>0.1</td>
<td>1.9</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>52</td>
<td>10.99</td>
<td>20.80</td>
<td>4.56</td>
<td>0.63</td>
<td>2.4</td>
<td>23</td>
</tr>
<tr>
<td>CA 72-4</td>
<td>52</td>
<td>3.34</td>
<td>10.49</td>
<td>3.24</td>
<td>0.45</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>AFP</td>
<td>52</td>
<td>2.58</td>
<td>0.13</td>
<td>0.35</td>
<td>0.05</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Ferritin</td>
<td>52</td>
<td>50.44</td>
<td>1847.5</td>
<td>42.9</td>
<td>5.96</td>
<td>7</td>
<td>176</td>
</tr>
</tbody>
</table>
We conclude that elevated PSA in elderly men increases due to the presence of a malignant tumour or not. The answer is not evident; after the age of 50, both prostate cancer and benign hypertrophy are very common, and the prevalence of hepatic, renal diseases or anaemia was low, and only 5.7% of the sample smoked. We may infer that the study sample was generally healthy.

The prostate specific antigen (PSA) deserves special mention; after the age of 50, both prostate cancer and benign hypertrophy are very common, and the incidence of both clinical entities increases with age. In benign hypertrophy, PSA values increase in direct proportion to the size of the prostate, with a wide range of values [37–39]. Up to 33% of the men studied had PSA levels above the cut-off, most of them (85%) with symptoms resulting from urinary tract obstruction. We conclude that elevated PSA in elderly men generally reflects a pathological condition, malignant or not.

If increased levels of the markers are not due to a greater prevalence of chronic diseases, are such increases due to the presence of a malignant tumour that is concealed or in a preclinical stage? The answer is no in most cases. The prevalence of increased markers studied is well above the incidence rates of tumours normally seen in the older population. Among the commonest tumours in elderly people are those of colon (incidence ratio of 45 per 10 000 per year) and breast cancer (38 per 10 000 per year) [4]. If we add the low sensitivity of the markers in subjects with no clinical evidence of cancer [8], we conclude that the increases are not related—at least directly—to the presence of the tumours with which the antigens are associated. The only exception may be prostate cancer. The prevalence of asymptomatic prostatic cancer is much greater than that of overt clinical disease and may affect 80% of octogenarian men [40].

It is possible that although increases in the markers in very old subjects do not reflect the existence of a tumour, they do bear a certain relationship to the oncogenic process. The point of contact may be the increase of multifocal hyperplasia occurring in old age, which rarely result in a clinical neoplasm [41]. Hyperplastic phenomena in the epithelial cells of the digestive tract [42] have been studied in detail, and a close relationship shown between gastric cancer, intestinal metaplasia and age, with a marked increase of precancerous lesions with ageing [43, 44]. In a recent study in asymptomatic elderly subjects with no known risk factors for suffering colonic or rectal neoplastic diseases, adenomas were found in 41% of the cases, a third of them with a moderate or severe dysplasia [45]. The histological study of rectosigmoid segments surgically excised in the presence of carcinoma showed areas of diffuse hyperplasia close to the tumour, leading to the hypothesis of a possible role of such changes in the carcinogenic process [46]. Similar phenomena are found in other tissues such as the pancreas [47], prostate gland [48], or breast [49], their frequency increasing with age.

A second possibility is that the markers simply reflect non-specific organic deterioration in elderly subjects. Benhamou et al. [50] have found elevated CA 19-9 serum levels in middle-aged diabetics with acute metabolic imbalance. Changes in antigen could be related to cell dysfunction or tissue damage, since the marker becomes normal only a considerable time after damage has been repaired. Other authors also relate the marker to tissue damage [51]. A longitudinal study of elderly people showed an association between CEA levels and mortality over 2 years or more [20]. Other similar studies have shown the relation between death and the lymphocyte count [52], or tumour necrosis factor [53]. In both cases the indices could be merely reflecting the degree of multisystemic impairment.

We believe that these data establish a starting point for subsequent longitudinal work that will allow several points of interest to be studied in depth. The follow-up of the subjects, the analysis of the pathological circumstances likely to arise and their relationship with the variables already analysed may provide an answer to the questions raised.
References


Authors' addresses

Hospital del Insalud, Soria, Spain

F. Fernandez
Residencia 'El Parque', Soria

M. Gutierrez
Hospital Clinico Universitario de Zaragoza, Spain

Address for correspondence: Louis Lopez, C/Rio Aragon 4/3-B, 50003, Zaragoza, Spain

*Received in revised form 1 June 1995*