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Abstract
The effect of age, cohort, and year of death on the mortality of cutaneous malignant melanoma is determined by the use of a Poisson log-linear model. During the period of the study, mortality due to this tumor increased exponentially (an annual rise of 11% in both sexes). The model attributes this rise to a cohort effect. The relative risk for the 1952 cohort as compared to the 1892 cohort is 530 for men and 280 for women. In the younger generations, no signs of leveling off are to be seen. The sharp increase in mortality due to malignant melanoma of the skin has also been witnessed in other countries and suggests a real increase in incidence. One explanation for this epidemic phenomenon lies in the progressive rise in exposure to UV radiation.

Introduction
There has been a rise in the incidence and mortality of CMM1 in the majority of white populations (1–3). The 1980, figures for Europe reveal that 16,500 cases were diagnosed in the 12 European Community member states and that there were 4,800 deaths from this disease. The number of cases in 1990 is reckoned to be 60% higher than that forecast 10 years ago (4).

Recent developments in statistical methods have made it possible for the influence of two kinds of factors to be assessed, i.e.: (a) those which act after a relatively long induction period, with ensuing differences in morbidity and mortality in the different generations; and (b) those which from the moment they appear exert an almost instantaneous effect on all age groups (5–9).

In Europe, Spain has one of the lowest recorded rates for incidence and mortality, with a position akin to the other southern countries (3, 4, 10). This article seeks to analyze mortality trends plotted for CMM in Spain by using Poisson log-linear models, with special attention being paid to the progress traced by the different generations in both sexes.

Materials and Methods
Mortality Statistics. The number of deaths due to CMM, broken down by age group and sex, were obtained from the annual figures published by the Instituto Nacional de Estadística (National Institute of Statistics). During the period of the study, 3 revisions of the ICD were in force in Spain. CMM corresponded to rubric 190 in the seventh and rubric 172 in the eighth and ninth revisions, introduced here in 1968 and 1980, respectively. For the purposes of rate calculation, recourse was had to National Institute of Statistics population estimates for the midpoint of each quinquennium studied.

Specific and Adjusted Rates. Age-specific and adjusted rates have been calculated for both sexes in each quinquennium, with the world population being taken as standard. Adjusted truncated rates for ages between 25–44 and 45–64 years have also been computed.

Age, Period and Cohort Model. On the assumption that the number of deaths in each age group and period was distributed as a Poisson variable, a log-linear model was used to assess the effect of age, year of birth, and period of death; the model was adjusted by using the General Linear Interactive Modeling computer package and the appropriate macros (6, 11). Given that mortality due to CMM is very infrequent among the very young, only the age groups over 24 (years) were taken into account for modeling purposes.

The predictive variables were sequentially included in the model. Age was taken first, since incidence and mortality from malignant melanoma increase dramatically with age. Next to be fitted was the "age + drift" model, which assumes a constant change in the rates logarithm between adjacent cohorts or periods. Thereafter the two-factor "age + period" and "age + cohort" models were considered. Finally, the model including all three factors—age, cohort, and period—was adjusted. These three variables are interdependent, which means that there is no single specific solution to this model and that additional constraints have to be imposed (identifiability problem). Of the solutions described in the literature, we opted for that proposed by Osmond et al. (5) and Decarli et al. (6). Cohorts and periods were defined according to their corresponding midpoints. Output age values are interpretable in terms of mean age-specific death rates for the period considered. Cohort and period-of-death values were averaged to unity.

Goodness-of-fit was evaluated on the basis of the deviance in each model. Deviance changes in the exclusively age-based model were tested for the contribution of the added factor. Pearson’s residuals were calculated for the final model and the assumed distribution checked by means of a normal quantile plot (12, 13). In addition, Filliben’s correlation test between predicted and observed distributions of residuals was carried out (14).
The estimators obtained from the final model are shown in the graphs. Cohort values linked to the earlier and more recent periods are based on fewer age-specific rates, hence proving less stable than central ones. Moreover, values for the most recent cohorts are based on a lower number of deaths.

Because the slope of the cohort effect cannot be separated from that of the period-of-death effect, some sources have proposed curvature analysis. Different definitions of curvature exist, however (7–9). The definition adopted here is that laid down by Holford: curvature is the deviation exhibited by each value estimated for a concrete cohort (or period) of the predicted value, taking into account the general slope of the cohort (or period) effect (9). The curvature values are independent of the solution chosen for the final model. Graphic representation of the pertinent curvatures enables local changes in the trends of said effects to be detected.

Results
Table 1 sets out age-specific CMM mortality rates, adjusted rates, and adjusted truncated rates for the 25–44- and 45–64-year age groups. Global mortality has increased almost 5-fold in the period studied, with an annual percentage rise of 11.0% in men and 10.7% in women being observed. The sex ratio remained at around 1.4.

In men, the rise in CMM-induced mortality follows a similar pattern both in the young adult group (25–44 years) and in the remaining adults (45–64 years), exhibiting a percentage increase of 15% per year. In women this percentage is 11% in the youngest group (25–44 years), rising to 13% in the 45–64-year age group. A substantial upswing is seen in specific rates for all age groups (Figs. 1 and 2). The right-hand sides of both graphs depict the cohort and period effects, averaged to unity and represented on a semilogarithmic scale. These effects are interpretable in terms of relative risk for a given cohort (or period), with the weighted average for all cohorts (or periods) being taken as reference. A pronounced cohort effect is in evidence from the earliest generations in the present century with no apparent trend towards stabilization. Excluding the first and the last cohorts (estimated on the basis of a single rate), the relative risk for the 1952 cohort compared to the 1892 cohort is close on 500 among men and 300 among women. The model indicates no signs of any leveling off in the younger generations.

The period effect is much less important, revealing an initial rise and a subsequent leveling off. In the last quinquennium, a slight drop in the period effect is to be observed in women, which is in line with a relatively more favorable prognosis for this sex.

Curvature values for the cohort and period effects in both sexes are shown in Fig. 3. The earliest cohorts exhibit values higher than those forecast for the general slope, a reading which accords with the profiles exhibited by these cohorts in Figs. 1 and 2. In the graph plotted for men, attention should be paid to the rising curvature traced by the most recent cohorts. For these generations, this implies an even greater increase in mortality than that forecast for the overall slope. Among women the situation is more stable, with fluctuations around unity. The curvature of the period effect in both sexes exhibits a marked increase in the second quinquennium.

Discussion
The results of our study point to a considerable increase in mortality due to this tumor across all age groups. On the basis of the model applied, the increase in mortality over time is principally attributable to a cohort effect. According to these results, the risk of dying from cutaneous malignant melanoma has been increasing over successive generations. This rise is quantitatively greater in men, a phenomenon which can also be explained by the relatively lower survival rates associated with males (15–17). Judging by the results obtained for the youngest cohorts, a leveling off in mortality would seem unlikely. The predicted increase is greater in men, a prospect likewise indicated by the curvature value for the lattermost points (Fig. 3). The period effect exhibits an
Fig. 1. Mortality due to malignant melanoma in men, Spain, 1967-1986. Specific rates by age group (top). Age effect estimated on the basis of the Poisson model (bottom, left) and birth-cohort and period-of-death effects (bottom, right). Age is in years.

Table 2. Goodness-of-fit test for different age-, period-, and cohort-specific models of cutaneous malignant melanoma in males and females in Spain, 1967-1986

<table>
<thead>
<tr>
<th>Model</th>
<th>Degrees of freedom</th>
<th>Deviance (males)</th>
<th>Deviance (females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36</td>
<td>436.1</td>
<td>369.0</td>
</tr>
<tr>
<td>Age + drift</td>
<td>35</td>
<td>49.9</td>
<td>41.7</td>
</tr>
<tr>
<td>Age + period</td>
<td>33</td>
<td>42.4</td>
<td>30.8</td>
</tr>
<tr>
<td>Age + cohort</td>
<td>22</td>
<td>29.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Age + period + cohort</td>
<td>20</td>
<td>17.2</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Using the same methodology, Osmond et al. (18) carried out an English study into mortality due to different neoplasms. With regard to CMM, the cohort effect they found was substantially less pronounced than that described in our study. Furthermore, their model did not predict a rise in mortality in the younger cohorts.
As mentioned above, the problem of identifiability renders it impossible for the slope of the period effect to be separated from that of the cohort effect (6–9). The solution proposed by Osmond, Gardner, and Decarli brings the model closer to resembling the best solutions obtained from the partial models (where the problem of identifiability is not present) without the need to choose any arbitrary constraints. This solution has been criticized as lending more weight to the cohort effect (9). However, as others in this field have pointed out, if one actually had to decide which of the two effects was responsible for the slope encountered, the cohort effect would probably be deemed more important than the period effect (19).

Studies on the evolution of CMM incidence in different populations always reveal a sharp rise in incidence over the course of the last few decades (10, 20–24). The softening in the slope of increase observed in the United States in recent years could in part reflect the growing rate of underreporting (25, 26), although a true leveling off cannot be excluded. In the literature, the majority is of the opinion that endeavors aimed at early detection partially account for this rise. Owing to diagnosis earlier on in the disease, survival is high.
Adjusted rate, truncated rates 25-44 and 45-64 years per 100,000 person-years using the world population as standard.

Contrary to this, however, is the CMM-induced mortality that climbing both in Europe (10) and in the United States (28). In the latter country, CMM is among the front runners as regards the increase seen in the period 1950–1980 (28). All the above data point to a real increase in incidence due to changes in the prevalence of the risk factors implicated.

In Spain there is no cancer register with nationwide coverage. Table 3 lists incidence rates furnished by the Registro de Cáncer de Zaragoza (Zaragoza Cancer Register), which has one of the longest series in this country. From this series it can be observed that between the first and last periods there was an annual increase of 16.3% in men and 13.8% in women. This increase is greater still if one looks at the 45–64-year-old age group (17.5% in men and 20.0% in women). The sex ratio has gone up, standing at 1.4 in the final period.

Our results demonstrate that the CMM epidemic is also present in Spain; indeed, it is this very tumor that has registered the greatest rate of rise in recent decades (29). The main etiological agent implicated is UV radiation, type B in particular, although type A may also be harmful (22, 30, 31). UV rays might have a dual role, acting as both initiator and promoter of the disease. Moderate exposure to sunlight seems to protect against the progress of CMM, as is borne out by the lower risk found among people who work outdoors (32, 33), whereas the effects of intense exposure are especially harmful, particularly during childhood (22, 30, 31). Lately, sunscreens have been said to produce a false sense of security about screening out UVB yet permitting the passage of UVA; the majority of people feel protected and so prolong the number of hours of exposure to the sun (30). Changes in sunbathing habits in Spain have meant that a sizable proportion of the population undergoes intense exposure during the summer months. The generalized spread of sunbathing coupled with the progressive depletion of the ozone layer might explain the marked cohort effect in this country. It has been suggested that for a 1% reduction in ozone, CMM might increase by 0.6% (36, 37). Hence, there is a need to insist on the elimination of chlorophenols and, from a public health standpoint, to advise the public to use protective creams along with other, more effective measures, such as avoiding the hours of greatest solar radiation (10 a.m. to 3 p.m.), during childhood in particular, and covering the most exposed areas to prevent sunburn.

Table 3 Incidence of cutaneous malignant melanoma in Zaragoza (Spain), 1968–1986*

<table>
<thead>
<tr>
<th>Period</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted rate</td>
<td>Truncated (25–44 yr)</td>
</tr>
<tr>
<td>1968–1972</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>1973–1977</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1978–1982</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>1983–1986</td>
<td>2.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

* Source: Registro de Cáncer de Zaragoza; Diputación General de Aragón.


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