Author's response to reviews

Title: Changes in period and cohort effects on haematological cancer mortality in Spain, 1952-2006

Authors: 

   Roberto Pastor-Barriuso (rpastor@isciii.es)  
   Gonzalo López-Abente (glabente@isciii.es)

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Author's response to reviews: see over
Dear Dr. Downing,

Thank you for the review and for the comments of the reviewers to the above mentioned manuscript. We thank you and the reviewers for the thoughtful comments and for acknowledging the relevance of our paper. We have prepared a revised version of the manuscript that takes all comments into account. In the response below, we provide itemized answers to each of the reviewers’ comments, including details on the changes introduced in the revised manuscript.

In advance, thank you for considering our manuscript for publication in *BMC Cancer*. I look forward to hearing from you.

Sincerely,

[Signature]

Roberto Pastor-Barriuso, PhD
National Center for Epidemiology
Carlos III Institute of Health
Monforte de Lemos 5
28029 Madrid, Spain
Tel.: +34 91 822 2359
Fax: +34 91 387 7815
e-mail: rpastor@isciii.es
Response to comments from reviewer 1

The authors address an interesting and important topic of increasing mortality trends for NHL and multiple myeloma, highlighting important differences between genders.

I suggest the following minor essential revisions:

1. Background, Paragraph 1:
   1. a. The word 'morbimortality' does not appear in the English dictionary, and should be changed to 'morbidity and mortality'.

   The word “morbimortality” has been changed to “morbidity and mortality” (page 4, line 3).

   1. b. The sentence beginning 'In Europe, Spain occupies...' would read better as follows: "Morbidity and mortality from haematological cancers in Spain are comparable to the European average" (see also discretionary revisions).

   As properly requested by the reviewer, we have reworded this sentence as “Morbidity and mortality from haematological cancers in Spain are fairly similar to the European average” (page 4, lines 3-4).

2. Background, Paragraph 2:
   2. a. Change ‘in contract’ to ‘in contrast’.

   This typo has been corrected (page 4, line 10).

3. Background, Paragraph 3:
   3. a. Change ‘potential distorting effects’ to ‘potential confounding effects’.

   The expression “potential distorting effects” has been changed to “potential confounding effects” (page 4, line 23).

4. Methods, Data Source:
   4. a. Last sentence should be rewritten as: “Mid-year population estimates for Spain were obtained from the Spanish National Institute of Statistics from 1952 to 2006 (insert reference here)”.

   The last sentence of the Data Source section has been rewritten as suggested (page 5, lines 16-18), adding the new reference 16 for the Spanish National Institute of Statistics website.

   4. b. The authors mention ‘problems of case ascertainment and death certification for lymphoid tumours from the beginning of cancer registry activities’ in the Background, paragraph 2 – it would be useful to further explore whether ascertainment of death certification is thought to be a problem for the Spanish data within the data source section and if so, this should also be added to the study limitations.

   According to previous validation studies, haematological cancer death certification in Spain was accurate during the 1980s and 1990s. Compared with clinical or pathological reports (gold standard), death certificates showed detection and confirmation rates of 86% and 80% for...
lymphomas, 96% and 94% for multiple myeloma, and 93% and 93% for leukaemia, respectively. This information is now included in the Data Source section of the revised manuscript (page 5, lines 13-16) along with the citation of the validation study (reference 17). Nevertheless, there is no information on the accuracy of death certification in Spain for the 1960s and 1970s and we cannot rule out some degree of under-certification of haematological cancer deaths during this initial period. This limitation is now explicitly stated in the revised version of the manuscript (page 14, lines 11-15).

I suggest the following discretionary revisions:

5. Background, Paragraph 1:
5. a. It would be useful if the authors listed European averages alongside the Spanish morbidity and mortality figures.

Incidence and mortality rates of haematological cancers in Spain are very similar to those observed for all 40 European countries:

<table>
<thead>
<tr>
<th>Haematological cancer</th>
<th>Incidence rate</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spain</td>
<td>Europe</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>10.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>8.3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Source: European Cancer Observatory 2012.

For the sake of simplicity, we have opted to list only the Spanish rates, indicating that they are fairly similar to the European averages. In addition, we have updated morbidity and mortality figures from 2008 to 2012 in the revised version of the manuscript (page 4, lines 2-7), together with the corresponding updated references 1 and 2.

6. Figure 1:
6. a. There is a lot of important information in Figure 1 and it may be more appropriate to produce separate plots for each diagnostic group showing both males and females.

We concur with the reviewer that Figure 1 is too heavy and cumbersome. To improve the presentation, we have produced separate plots for each haematological cancer displaying time trends in both men and women (see revised Figure 1).

Response to comments from reviewer 2

1. Is the question posed by the authors well defined? Yes.

Thank you. No response is needed.

2. Are the methods appropriate and well described?
The approach in this manuscript is very challenging and the idea sounds good, but I think there are partly questionable the method they used.
We agree with the reviewer that the methodological approach is challenging, but we believe it is appropriate for the identification of significant trend changes in period and cohort effects. Responses to specific comments are provided below.

**Major Compulsory Revisions:**

2. **a.** As authors mentioned in the last sentence of the Methods section (page 7), it is doubtful whether the estimated period or cohort effect can be applied to Joinpoint regression model. The idea seems good, but the statistical adequacy needs to be well explained in the method part in more detail.

As indicated by the reviewer, further methodological details on the validity of joinpoint regression analyses of period and cohort curvatures have been added at the end of the Methods section (page 7, lines 16-21 and page 8, lines 1-9). In particular, we have paid special attention to justifying that, although the specific slopes within each segment cannot be determined, the changes in period and cohort slopes at the change-points remain estimable from curvature components. The text now reads as follows:

“Specifically, the joinpoint regression model for the period curvature \( \tilde{\beta}_p \) with a single significant change-point \( \tau \) was

\[
\tilde{\beta}_p = \beta_0 + \beta_1 p + \beta_2 (p - \tau) + \epsilon,
\]

where \((p - \tau)_+ = p - \tau\) if the period \(p\) is above the change-point \(\tau\) and 0 if \(p\) is below \(\tau\) and \(\epsilon\) is the error with mean 0 and heterogeneous variance \(v_p\). To interpret joinpoint regression coefficients, we added back the period linear trend to the period curvature from the above joinpoint model and obtained the two-segmented period effect

\[
\beta_p = \beta_0^* + (\beta_1 + \beta_1 + \beta_2) p + \beta_2 (p - \tau) + \epsilon,
\]

where the intercept \(\beta_0^* = \beta_0 - \beta_1 \overline{p}_w\). The parameters \(\beta_1 + \beta_1\) and \(\beta_1 + \beta_1 + \beta_2\) represented the period slopes below and above the change-point \(\tau\), respectively, which were not estimable since the overall period slope \(\beta_1\) cannot be uniquely determined. However, the change in period slopes at the change-point can be estimated directly as the coefficient \(\beta_2\) from joinpoint regression analysis of period curvatures. Similar arguments can be applied to cohort effects, as well as to the presence of multiple change-points.”

**Minor Essential Revisions:**

2. **b.** The authors showed the results of the Joinpoint regression model of age-adjusted mortality in the first paragraph of the Results section (page 7). But they have not explained in the Methods section.

Joinpoint regression models were not applied to age-adjusted mortality rates. In fact, the annual percent changes (APCs) showed in the first paragraph of the Results section refer to net drifts (sum of period and cohort linear slopes) over the entire study period, as obtained from the standard age-period-cohort models (already explained in Methods). To further clarify this point, we have included the expression “APCs in age-adjusted rates over the entire study period” at first appearance in the initial paragraph of the Results section (page 8, lines 17-18).
3. Are the data sound?

Discretionary Revisions:

3. a. It is good that the authors used very long-term mortality data, but we need to think about data quality in the earlier period (1950s). In addition, although authors mentioned the accuracy of death certificate data during the period 1980-2002, the data from other period should be assured the quality of data. Or they may be able to do sensitivity analysis using data whose quality was assured.

As indicated in our response to reviewer 1 (point 4.b), haematological cancer death certification in Spain has been shown to be accurate from 1980 onwards, with detection and confirmation rates well above 80% for all haematological tumours (page 5, lines 13-16 of the revised version). However, there are no validation studies on the quality of death certification in Spain before 1980 and we cannot rule out some degree of under-certification during the initial period, as explicitly stated in the Study Limitations section of the revised manuscript (page 14, lines 11-15). In addition, to explore the potential impact of under-certification on the observed time trends, we performed sensitivity analyses excluding deaths during the initial 5-year periods 1952–1956 and 1957–1961 and results remained nearly the same (see figures below). These sensitivity analyses are outlined in the revised version of the manuscript (page 14, lines 15-18).

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data?

Major Compulsory Revisions:

5. a. For the aim of this study, probably the authors need to add some other statistics, such as incidence, survival of haematological cancer. Even if these data were not available for the national level and all study period, they could find some supportive data from regional cancer registry data. The results were not fully interpreted and explained well, because they showed and thought about only mortality trends.

As already recognised in the original manuscript, one of the main limitations of the study was the lack of long-term incidence data for the entire country, since most regional cancer registries began their activities in the mid-1980s and covered only one fourth of the total Spanish population. Nevertheless, our countrywide mortality findings are perfectly consistent with previous studies on the incidence of non-Hodgkin’s lymphoma in selected Spanish regions. These studies reported a recent attenuation of the epidemic increase in the incidence of non-Hodgkin’s lymphoma, which was mainly attributable to the full implementation of modern diagnostic imaging techniques. We have incorporated this external evidence, along with citations of the published papers, to strengthen the discussion on haematological cancer trends in the revised manuscript (page 12, lines 9-13).

6. Are limitations of the work clearly stated? Yes.

Thank you. No response is needed.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.

No action needed.

8. Do the title and abstract accurately convey what has been found? Yes.

Thank you. No response is needed.

9. Is the writing acceptable? Yes.

No action needed.

Response to comments from reviewer 3

Major Compulsory Revisions:

1. The authors adopted the approach proposed by Holford to overcome the problem of non-identifiability of model parameters arising from the exact linear dependence among age, period, and cohort. Can the authors explain what advantages Holford’s approach has over other APC models? For example, the author should at least compare the model used in the manuscript to that described by Yang Yang et al.
To overcome the non-identifiability problem in age-period-cohort models, we adopted Holford’s approach and restricted the summary of results to estimable effects, such as the net drift (sum of period and cohort linear slopes) and the period and cohort curvatures, because these parameters remain invariant irrespective of the particular approach used. Other solutions to the non-identifiability problem, including the approaches proposed by Osmond and Gardner, Decarli and La Vecchia, and Yang et al., go one step further and try to split the net drift into specific cohort and period linear slopes by imposing implicit statistical constraints on the parameter space. Leaving aside well-known criticisms on their ability to recover the true linear slopes, all these methods provide identical curvature components to those obtained from Holford’s approach, since curvatures are uniquely determined by the data. Given that changes in period and cohort effects are directly estimable from curvature components (see response to point 2.a of reviewer 2), study results would remain the same regardless of the approach used. This fact is now stated in the Methods section of the revised manuscript (page 6, lines 9-12).

2. The change-points for Non-Hodgkin’s lymphoma as provided by join point models (Figure 4) differ in men and women. Please Explain.

As pointed out by the reviewer, the downturn in mortality from non-Hodgkin’s lymphoma for recent cohorts took place in 1954 among women and later in 1968 among men. This male delay was mainly due to the fact that men born around 1960 were most affected by the HIV epidemic derived from injection drug use. This explanation has been added to the Discussion section (page 10, lines 17-20).

Discretionary Revisions:

3. According to the authors, the consistent male excess mortality across all calendar periods and age groups points to the importance of possible sex-related genetic markers of susceptibility in haematological cancers. Can the authors comment if there is a possible association between ethnicity and haematological cancer mortality?

Although there is recent evidence suggesting that the risk of haematological cancers varies greatly by ethnic group (see, for example, Shirley MH et al, *British Journal of Haematology* 2013, 163:465–477), most of the study population was of European Caucasian origin (96.6% according to the 2001 Spanish Census) and hence we were unable to compare haematological cancer mortality rates across ethnic groups.