Author's response to reviews

Title: Burden of disease due to cancer in Spain

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Author's response to reviews: see over
Dear Editor,

Thank you for considering our original manuscript entitled “Burden of disease due to cancer in Spain” for peer review process.

We would like to thank the reviewers for their valuable comments. We have sincerely appreciated their content and have found them extremely useful. Our answers to these comments are listed below and the revised version of the manuscript according to the reviewers’ comments is submitted.

We hope these changes meet with your approval and if you require any further changes to the manuscript please do not hesitate to contact me.

We look forward to your editorial decision.

Sincerely,

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Response to reviewers

Reviewer: Michelle Elisabeth Kruijshaar

Major comments:

- Several of the results presented (e.g. cancer ranks second, ranking of different types of cancers, and even partly the age distribution) merely seem to emphasize what was already known, rather than add to our knowledge. It is important in writing up this study, to emphasize what this analysis adds and to give less prominence to results that follow what was already known. I think it is possible to make this paper much more interesting for the general reader. Also some editing is required to improve the English.

Thank you for these valuable comments. Some changes have been made in the manuscript and tables in order to highlight what this study adds to the cancer epidemiology knowledge. We have changed Table 2 and Figure 3 and we have added some new paragraphs in the background and discussion sections.

We have also tried to improve the English.

- I was surprised by the fact that no cancer incidence data for 2000 were available. I seem to recall that incidence data for 1996 from regional cancer registries (& hospital statistics) were available in 2001, hence expecting 2000 figures to be available by now. Could the authors explain this? One of the conclusions of the paper is that ‘it highlights the need for the coverage of Spanish tumour registries to be increased”’. This issue, however, is not discussed in the main body of the discussion, nor is it emphasized in the results or elsewhere in the paper. This needs to be addressed.

In Spain there is not a National Registry of cancer. Indeed, data from registries come from some but not all the regions in Spain, so we made our own estimation, based on validated previous incidence data and taking into account variability between regions.

Some Regional Registries publish their own data in local bulletins; however their definitive incidence figures are collected and published by the IARC. Incidence data for the period 1997-2001 have been published by IARC in December 2007\(^1\). Thus, at the time of the study realization, incidence data for 2000 from Spanish registries were not available.

We have included an explanation about the population coverage of the Spanish Regional Registries in the discussion section (paragraph 9).

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Detailed comments:

Abstract

- EUROCARE-3 study is mentioned here, but in the methods the Victorian burden of disease study is cited?

The EUROCARE-3 study is mentioned in the abstract as a source of information to estimate disease duration (the same as in the main text). The Victorian burden of disease study is cited in the text as a source of data about disability weights. In the abstract, we had referred to this study and to the Dutch study as “published weights” for space constraints. We have changed this expression in the abstract in an attempt to avoid misinterpretations.

Introduction

- Restructuring is required. A lot of information is given on what DALYs are and why they could be useful in general. However, it is not mentioned exactly why they are so useful for this study in particular. What does this study add to the evidence base/ what information does it provide to policy makers or physicians?

We have restructured and modified the introduction following the valuable given recommendations. We have tried to highlight that this study could give information about the disability caused by cancer, which is an important issue also in this disease, and that has been less studied than mortality. In addition, results of this study could serve as a source of information for other studies, such as those focusing on BoD attributable to risk factors or on the over time evolution.

- The large amount of information regarding which cancers are the leading causes of morbidity and mortality could be partially omitted to shorten the introduction.

We have removed some sentences related to this aspect.

Methods

- Why was age-weighting applied? It has been shown by Barendregt et al that the age-weighting used in the original GBD study has some flaws?

The age-weighting application is a controversial aspect of the DALY calculation. The GBD applied this weighting based on a number of studies that have indicated there is a broad social preference to value a year lived by a young adult more highly than a year lived by young child or at older ages. The influence of age-weighting on the ranking of conditions has not been very great in other studies. We applied age-weighting because of the previous reasons and in order to make results more comparable with those of other studies. Indeed, we have made a sensitivity analysis in order to assess the influence of age-weighting on the ranking of cancers and we have obtained almost the same result (the only difference has been that without age-weighting, Non-Hodgkin Lymphomas ranked 10th and brain cancer 11th, instead of 11th and 10th, respectively, with age-weighting).
- The second paragraph (data sources) could be condensed.

We have slightly abbreviated the second paragraph, about data sources. We considered to condensate it more, but we think that the information on this paragraph could be important for the reproducibility of the study.

- Reference 16 at the end of the second paragraph is duplicated/wrong.

Thank you for your attentive review. We have corrected the reference at the end of the second paragraph, which effectively, was wrong.

- The third paragraph (disease model) could be made clearer.

We have tried to make this paragraph more understandable.

- The second para of page 6 (variables used) could be combined with the very first paragraph of the methods.

We have included part of the second paragraph of page 6 in the first paragraph of the Methods.

- Incidence of 1997-2000 was estimated - see earlier: why was this necessary? And if the study is based on 2000 incidence data, why was incidence estimated for the period 1997-2000?

As we have explained in the response to the second comment (see above), in Spain there is not a National Registry of Cancer. Having data from some but not all the regions in the country made necessary to estimate national figures, which were based on available information and took into account variability between regions.

Incidence data were estimated for the period 1997-2000, in order to obtain stable and robust estimations by age and sex. For some cancer sites, the numbers of new cases in some age groups are very small and it is necessary to combine more than one year to obtain robust incidence data estimations.

- Survival data from the US were used, would the authors expect similar figures for Spain?

The ratio between survival at 5 and at 10 years ($S_5/S_{10}$) from the US was applied to the survival at 5 years in Spain, in order to estimate the survival at 10 years, which was not available for some tumour sites. This follows the methodology proposed by the WHO.

We have assumed a similar ratio between survival at 5 and at 10 years for Spain and the US. We think that crude survival data may differ slightly between Spain and the US, but that the ratio between survival at 5 and at 10 years can be assumed to be similar.

Results

- Additional file 2 is referred to in the text – is this going to be a web-file?

Yes, our intention was it to be a web-file.
- I am not sure all the information provided in table 1 is really required, e.g. by sex could be omitted? To which stage of the disease do the duration and weight provided this table refer? Or do they give an overall weighted average across the disease stages, in which case the footnotes need to explain how this was estimated.

We think that, even if giving data by sex is not indispensable, this information can be useful for other epidemiological studies and contributes to the reproducibility of our study.

The duration data presented on the table correspond to the average of duration in patients who die of cancer and in patients who will be cured, weighted by the cure rate.

The disability weights on table 1 are the average of the disability of each disease stage, weighted by its duration and then by the cure rate.

We have added an explanation in the footnote of the table.

- Total number of DALYs do not mean much to many readers, and it would therefore be helpful to include proportions (not only for men and women but also for YLL and YLD) as well as the DALY per 1000 population as done in the discussion.

Thank you for this useful suggestion. We have made some changes in Table 2: we have omitted data of YLL and YLD, which are displayed in Figure 2, we have separated columns by sex and we have added DALY rates per 100000 population in order to present more meaningful data.

- It would be helpful to rank the cancers in Table 2 by order of largest number of DALYs.

We have arranged cancer sites by number of DALYs.

- ‘By type, the highest number of YLL was accounted for by lung cancer …’ It is not clear that this refers to men only - the statement ‘in the case of men’ needs to be placed earlier in the sentence.

We have condensed paragraph 3 and changed the sentence starting by “By type, the highest number of YLL…” and we think that now it is clearer than in the previous version of the manuscript.

- Figure 2 is much more informative than table 2, as is paragraph 4 compared to para 3. I would start with para 4 and omit parts of para 3 and possibly table 2.

Thank you for your suggestions. We have modified table 2 in order to make it more informative to the reader and we have condensed paragraph 3.

- The section on the distribution by age is very elaborate. Please condense this.

We agree with you that this section was too elaborate. We have modified it and we think that it is clearer now. We have also changed figure 3, in order to give complete information about age distribution for all cancer sites.
Discussion

- Please give more focus to what this study adds to our knowledge/understanding.

Thank you for this valuable comment. We have made some modifications to the discussion section: We have slightly condensed paragraph 2 and have added some sentences explaining the differences in the ranking of cancers when using mortality data compared to using BoD data. We have also added a paragraph which highlights the importance of disability in some cancer sites (paragraph 3) and highlighted some of the results related to age distribution (last part of paragraph 4).

- Cancer ranks no 2. Maybe the authors could state the no 1 as well?

We have added the information about the leading cause of DALYs in Spain, both in the abstract and in the main text.

- Consistency with other figures: please add the year to which the WHO Euro-A estimates refer to. Rounding of proportions: 15.8% is 16%.

Thank you for this remark. We have specified the year to which the WHO estimates refer and have rounded of proportions.

- Paragraph 2 could be condensed. The last part of this para (in the Euro-A region …) seems to be a different issue.

We have modified the 2nd paragraph in order to give more focus on aspects added by the study. We consider that the last part (“in the Euro-A region…”) was in line with previous sentences, all of them related to the comparison between our results and those of other studies: Australia, New Zealand and the Euro-A region of the WHO. We agree with you that it could be a different issue with respect to the first part of the paragraph and accordingly, we have moved this part to paragraph 6.

- Para 3 is kept nicely concise and ends with an interesting potential future consequence. This is the kind of style and messages that could make the paper more interesting for the general reader.

Thank you for this positive comment. We have tried to include more paragraphs with this kind of messages.

- Para 4. It is not clear in all parts whether the statements are in general (for all diseases) or just about cancers. In general women live longer so are likely to have more life years with disability, not necessarily only for cancers.

Thank you for this remark. We have specified that we were referring to cancers only.

- Para 5. Please omit ‘not accompanied by good QoL’. It is not necessary to add this as an improvement in survival would decrease the number of YLL, reducing the YLL:YLD ratio (or: increasing the importance of YLD), irrespective of whether YLD increase or not.

We have removed “not accompanied by good quality of life” from the 5th paragraph.
- How do the estimates of the different cancers compare to earlier estimates – if any are available. Are there any changes over time suggestive of improvements?

We have not made comparisons with earlier estimates in our country, because this is the first study carried out with this methodology in our setting. With respect to data from other countries, most of them refer also to 2000, which makes it impossible to study the over time evolution.

One of the objectives of this study is precisely to be a point of reference for future BoD estimations.

- A discussion on the coverage and possibly also the ‘up-to-date-ness’ of the incidence data needs to be included.

We have included in the discussion an explanation about the coverage of the Spanish registries (paragraph 9). With respect to the ‘up-to-date-ness’ of incidence data, we have also included a general explanation about the validity of data for 2000 (paragraph 7).

- The last part of the conclusion (‘the difference in the weight …’) would be better placed elsewhere in the discussion, as it does not give a particular take home message for the reader.

We have moved this part of the conclusion to the last paragraph of the discussion.

Reviewer: Duncan Mortimer

Major essential revisions:

- Burden of Disease (BoD) for priority setting: The authors contend that the “results of BoD studies can serve as a source of information for allocating resources” (p2) and that “information on type-specific cancer burden of disease is important for prioritizing interventions designed to optimize health benefits for the population” (p2). Note, however, that a number of authors have previously argued that BoD studies are uninformative for priority setting (e.g. Mooney & Wiseman, 2000; Shiell et al, 1987; Wiseman & Mooney, 1998). Specifically, many health economists would maintain that identifying the size of a problem is no help at all in working out how best to address a problem. Knowing that cancer is the second-leading cause of DALYs in Spain and attributing this burden to specific cancers tells us nothing about the extent to which this BoD can be reduced or about which interventions would provide the best means of obtaining such a reduction. At a minimum, the section summarizing relevant background information should recognize the existence of such views.

Thank you for this valuable comment. We have included a short comment in this sense in the last paragraph of the discussion section, and we have also softened our statements about the applicability of BoD data to priority settings in the abstract and in the main text.
- Policy relevance: Setting aside arguments regarding the usefulness of BoD estimates for priority setting, it could be argued that BoD estimates for the year 2000 are now of purely historical interest for any purpose. The authors should therefore provide a justification for using year 2000 data. Are more up-to-date data available or likely to become available in the future for some or all components? If not, then BoD estimates won’t be of much use for tracking changes in epidemiology and monitoring progress over time. Evidence or argument regarding the continuing policy relevance (or otherwise) of BoD estimates for the year 2000 should therefore be presented (eg. Is the epidemiology of cancer stable over the period 2000 to 2008? Is best practice for cancer care the same in 2008 as it was in 2000?).

This is an important issue, which affects not only to BoD estimates but also to many other health indicators. For the component of mortality, more up-to-date data are available. In the case of incidence data, some Regional Registries publish their own data in local bulletins and are available for the year 2002 or 2003; however their definitive incidence figures are collected and published by the IARC. Incidence data for the period 1997-2001 have been published by IARC in December 2007.

We have added a short comment with respect to the changes in cancer epidemiology and in best practice for cancer and their potential influence on BoD estimates. We have not included a detailed analysis of these interesting aspects because it would be necessary to include a large explanation to reflect changes in each cancer site (paragraph 7).

In addition to the lack of more recent available data, one reason to study BoD for the year 2000 is that it allows us to compare our results with those of other studies, given that most of them report data for this year. Data for 2000 can also serve as the point of reference to study changes over time. We have added some comments in this line in the discussion section (paragraph 7).

- Applicability of disability weights to Spanish population: Recent evidence from the European Disability Weights project (eg. Essink-Bot et al, 2002; Schwarzinger et al, 2003) suggests that cross-country variation in disability weights might be significant even across relatively wealthy Western European nations. The authors claim that, despite the potential for variation in disability weights, cancer BoD calculations will be insensitive to variation in disability weights and cite Krujishaar & Barendregt (2004) in support of this claim. In the Krujishaar & Barendregt (2004) study, replacing EU weights with country-specific weights increased breast cancer DALYs from 741.9 to 764.1 for Spain but reduced breast cancer DALYs from 801.4 to 763.7 for France. While these variations in DALYs are relatively minor (predominantly due to the fact that 70% of the total burden of breast cancer is attributable to premature mortality rather than YLDs), not all cancers have the same proportion of DALYs attributable to premature mortality. At a minimum, the authors should recognize that the use of country-specific disability weights might alter the ranking of neoplasms by burden, as well as the absolute burden for cancer and each cancer type.

We agree with you that different disability weights might modify the absolute number of DALYs and even the ranking of tumour sites. We had cited the study Krujishaar & Barendregt (2004) which reports that using different disability weights had not major effects on the BoD due to breast cancer. Given that breast cancer is one of the cancer sites with a higher YLD/DALY proportion, we had considered that we could reasonably extrapolate this conclusion to all the neoplasms. Nevertheless, we agree with you that it was necessary to better
explain this point and we have modified the corresponding paragraph in the discussion section in order to give a more detailed explanation (paragraph 8).

- Modeling: Very little detail has been provided regarding methods or results for predicting incidence and duration. There is therefore insufficient detail in the paper to peer-review these aspects of the study.

Methods used for predicting duration are those described by the WHO in the reference 18 of the manuscript. We have tried to give a general description of these methods and have cited the WHO paper for more details. In the same way, we have cited references 9 and 21 for more detailed description of the methodology for incidence estimation.

Our opinion is that giving a more detailed description of the methods would make too large the Methods section and that there is sufficient information to reproduce the study. However, if you could tell us some specific feature for which you think that more detail must be given, we will be very grateful and we will add it to the text.

- Sampling error and parameter uncertainty: Sensitivity analysis has not been performed to reflect parameter uncertainty and confidence intervals have not been provided to reflect sampling error. Some attempt should be been made to communicate the extent of uncertainty associated with the BoD estimates reported in the paper.

Thank you for raising this important issue, which has been extensively studied mainly in GBD studies, where quality of data sources in many countries is very low, compared to developed countries. In line with your comment, we have added a more detailed discussion about parameter uncertainty in the text (discussion section, paragraph 9). We have also made a sensitivity analysis to assess the influence of age-weighting on DALY estimations in our study, and it has shown that, for some cancer sites, absolute numbers change but the ranking of cancer sites remain almost equal (the only difference being that, without age-weighting, Non-Hodgkin Lymphomas ranked 10th and brain cancer 11th, instead of 11th and 10th with age-weighting).

With respect to sampling error, we have not included any comments, because the precision of the YLD estimates is not quantifiable in the usual statistical sense of deriving a confidence interval, because of the diversity of the data sources used.

**Minor essential revisions:**

- Assumptions: At least one assumption has not been supported by either evidence, argument or expert opinion. Specifically, “…disease duration… for the group of patients who were cured… was set at 5 years” (p6).

Thank you for this remark. This assumption might be arguable, because some cured cancers may have some grade of disability for more than 5 years; however, we set the disease duration for the patients who survive at 5 years, following the disease model of the WHO, which has been also applied in posterior studies. We have added in the text that this assumption is based on this disease model.
Reviewer: Seok-Jun Jun Yoon

Methods

- To estimate this type of burden using DALYs, essential process is to calculate their own
disability weight (DW). However, this paper were based on those of the Dutch study. It needs
more detail evidence and description regarding similarity of DW between Spain and Holland.

We agree with you that disability weights are an important feature to estimate BoD. We have
added more details on the text about some reasons to use the disability weights of the Dutch
study (paragraph 8). We had cited the study Krujishaar & Barendregt (2004) in order to support
our opinion that in the case of cancers, the influence of disability weights could be minor. That
study estimated the BoD due to breast cancer in six European countries (including The
Netherlands and Spain) and reported that using country-specific weights had not major effects
on the BoD for this cancer site. Given that breast cancer is one of the cancer sites with a higher
YLD/DALY proportion, we have considered that we could reasonably extrapolate this
conclusion to all the malignant neoplasms.

Results

- This paper should avoid duplicate description between table 2 and figure 2, 3. Figure 1 does
not need for this paper.

Thank you for this suggestion. We have made some changes in Table 2 and in Figure 3, and
now, there is not duplicate information between them.

With respect to Figure 1, we think that, even if it is not indispensable, it might be helpful to
understand the disease model and the methods used to estimate YLDs. For this reason we would
prefer not to remove it.

Discussion

- Discussion section needs more expansion regarding implication and limitation of this study.

As suggested, we have made some changes in the discussion section, giving more detail about
limitations of the study (paragraphs 8 and 9) and about their possible implications and
applicability (paragraphs 3, 4 and 7).