Author’s response to reviews

Title: Estimating and validating disability-adjusted life years at the global level: a framework for cancer

Authors:

Isabelle Soerjomataram (soerjomatarami@iarc.fr)
Joannie Lortet-Tieulent (tieulentj@iarc.fr)
Jacques Ferlay (FerlayJ@iarc.fr)
David Forman (formand@iarc.fr)
Colin Mathers (mathersc@who.int)
Donald Maxwell Parkin (max.parkin@ctsu.ox.ac.uk)
Freddie Bray (brayf@iarc.fr)

Version: 3 Date: 16 April 2012

Author’s response to reviews: see over
Author’s responses to reviewers

Title: Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer

Manuscript number: 1829693851605747

Version: 1 Date: April 16, 2012

Author's response to reviews: see over
Reviewer's report
Title: Estimating and validating disability-adjusted life years at the global level: a framework for cancer

Version: 1 Date: 4 November 2011

Reviewer: Kaliannagounder Krishnamoorthy

Reviewer's report:
1. Is the question posed by the authors well defined?
Yes. The authors attempted to identify and quantify the variables, proposed a framework for more realistic estimates of cancer. The questions including the validation of variables and estimates based on various sources are well defined and justified.

No response required

2. Are the methods appropriate and well described?
Person trade off method was used to derive DW. The groups based on health outcomes of cancer following diagnosis and with or without treatment were well described. However, the authors need to mention whether any assumption was considered for the morbidity among cured.

We have now addressed the reviewer's comment and included text on the assumptions and implications concerning the morbidity among the cured and also covered other assumptions and limitations that may pertain to this study (see Discussion sections, pages 17-19).

Sensitivity analysis on different assumptions (proportion treated vs observed treatment, two stage vs three stage natural history, advanced cancer as a proxy for untreated and impact of discount and age weight) is appropriate to test the behavior of the model.

No response required.

3. Are the data sound?
Data (primary) on the derived DW are sound. For the estimates of DALY, only secondary data (epidemiological) were used, with its own limitations on the quality and under reporting. The assumptions related to the data source are addressed through sensitivity analysis.

No response required.

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

No response required.

5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes. The discussions and conclusions are well supported by the data and the outcome of model exercises.

No response required.
6. Are limitations of the work clearly stated?
The limitation of the estimate by using DW for different sequale of treated cases of cancer is to be mentioned as it does not reflect the natural history of disease progression. The treatment (quality) varies with health facilities in different countries.

We agree with the reviewer, as has been pointed out, treatment quality and support for patient’s during follow-up differ between countries and most probably is worse in less developed countries. Common weights may not capture the differing in functionality or quality of life among patients diagnosed and treated with cancer in different countries. We have now included text on this limitation on pages 18-19 of the current version of our discussion section.

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

No response required.

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

No response required.

9. Is the writing acceptable? Yes The legend for the figure 2 should be self-explainatory

We have now added a title to the x-axis of Figure 2.
Reviewer's report
Title: Estimating and validating disability-adjusted life years at the global level: a framework for cancer
Version: 1 Date: 27 January 2012
Reviewer: Jennifer Margaret Jelsma

Reviewer's report:
The authors are to be congratulated for producing a plausible estimation of the BoD attributed to cancer. This is important information which needs to be published. However, the paper itself is somewhat dense and difficult to read. I have the following suggestions.

1. Suggest splitting paper into two.
The paper is rather confusing as it presents a large amount of data, and wishes to achieve two goals, estimation of the BoD related to different types of cancer in different countries and to document the methodology used, including a simpler method of calculation. By presenting both in the current paper, the authors overwhelm the reader. It is suggested that the authors divide the paper into two, one of which explores the use of the two stage model (as opposed to the three stage model) and describes the methodology in more detail, including the formulas used to calculate YLDs and YLLs. The other paper could usefully concentrate on the results and comparisons across different types of cancers and across countries. In other words, I am suggesting that the authors present one paper on methodological issues, which would include sensitivity analysis and a paper on the BoD in the 184 countries which are referred to in the Introduction but whose BoD is not presented or discussed.

The first might be more appropriate for BMC Research Methodology, the second for BMC Medicine. This is a strong recommendation but an editorial decision and hence not a compulsory revision.

We agree with the reviewer that there are a lot of issues that the paper addresses and presents. We think it was good to be comprehensive, and our paper is intended to describe the methodological framework, with the results for the 4 countries representing each of the four human development categories and serves as case studies to compare results with earlier WHO estimations. We have now clarified the goal of the paper, and deleted the (confusing) references to global estimation (‘184 countries’), both in the Introduction and Abstract.

2. If the paper is not split, the objectives need to be made clearer - presenting the development of the BoD estimation methodology, sensitivity analysis, comparison of the estimation for 4 countries etc. (Unclear why the 184 countries are mentioned in the Abstract as these data are not presented or discussed at any stage.)

We have now clarified the objective and references to global estimation (‘184 countries’), both in the Introduction and Abstract. (see also response to reviewer’s first comment above)

3. It would be useful to include the formulas used to calculate the DALYs, so that those not familiar with the methodology can appreciate the importance of correct estimation of incidence, duration, severity.
We have now included the formulas used to calculate YLLs, YLD and DALYs in the method section page 6.

4. The Discussion and Conclusions should similarly be divided up into a critique of the methodology and clear recommendations as what parameters to use (e.g. 2 or 3 stage model) and whether to employ similar bases for calculations in future studies. As a new global study might be planned, this information would be very valuable.

We have now incorporated this recommendation from the reviewer. A list of assumptions and limitations are now added into the manuscript. The final conclusions also include remarks on possible improvements in the approach, if national burden of disease studies are is to be done with better data.

5. It would be interesting to compare the results of the DALY calculations with the Global BoD figures, although possibly outdated. There is also room to compare and contrast the individual country results in more detail than is currently presented.

Reviewer 3 has suggested a similar idea, therefore we have now added one additional graph (Figure 4, discussed on page 16 of current manuscript) comparing the DALYs as reported by WHO for the four countries that we presented in this study. The WHO-reported DALY rates were discounted and age-weighted, so that the rates shown in the figure are generally lower than the reported rates in Figure 2. Although WHO calculation was performed based on 2004 data[1] (and ours on 2008 data), we found very similar results e.g. in terms of gradient and ranking of cancer-specific site. Some observed differences are probably related to the change in incidence or mortality rates over the past few years. For example the DALY for lung cancer for Norwegian men was larger in the WHO results while the reverse was seen for Bulgaria. This is in accordance with the trend of lung cancer in both countries[2]. Differences were also observed for cancers that contributed to a large burden of YLD such as breast, prostate and cervical cancer. In our study we incorporated long-term effects of treatment e.g. mastectomy for breast cancer which increased the DALY estimate. Such an observation was seen for cervical cancer especially in India and Zimbabwe, where the burden from this cancer is large (and had probably been under-estimated in the original GBD study).
Reviewer's report
Title: Estimating and validating disability-adjusted life years at the global level: a framework for cancer
Version: 1 Date:
Reviewer (#3):

Reviewer's report:
I have read this manuscript with great interest. The topic addressed in the paper is relevant and interesting. The cross-country comparison is very fascinating and the findings are very interesting.
This is a relevant and relatively well written paper. However, the authors should consider the following in order to make the paper more accessible to a reader who may not be familiar with the topic.

Major Revisions
Background
The authors need to justify, upfront, why this study was important, in view of the global burden of disease study. Some of this information is provided in the discussion but I would suggest that it is presented in the introduction.
Response to the following questions would strengthen the justification;
- What does the paper add to the existing GBD information? Does it update the information? Does it improve on the methods? The authors say “they adapt and improve” on the GBD methodology—in which ways—does this produce better estimates?
- Some of this information was put in the discussion but would benefit from benefit from being presented upfront.

*We have now incorporated the reviewer’s suggestion and added a paragraph on the extra value of this study in the view of earlier works done in the area in the introduction (page 3).*

Methods
While the authors provide a very transparent and accessible description of the methods, some assumptions were made which would require reflection.
- It would be useful to explain/reflect on the validity of the estimates provided by GLOBOCAN ....especially in the case of low and middle income countries.

*We have now added a section on the validity of the GLOBOCAN2008 estimates at page 17-18 of the discussion section. As the reviewer pointed out GLOBOCAN presents *estimates* of the cancer burden and the accuracy varies depending on data availability in those country. A much more detailed discussion on the method of estimation for the GLOBOCAN2008 has been described in the cited paper (reference 2) from Ferlay et al [3].*

- Other than data availability, it is not clear why the proportion cured (5yrs survival) was based on a Norwegian cancer registry. While this may be useful for the other high income countries, it may not apply in low income countries. This pattern is followed in most assessments. While the limitations of lack of data in low income countries is appreciated, a concrete reflection on using these estimates should be discussed as part of the limitations (which are incidentally missing in the paper).
In fact, we did not apply proportion cured from Norway to all countries. We used the proportion cured as reported in Norway to *extrapolate* country-specific proportions from 5-year survival estimates. This is now made clearer in the Methods section.

- While in epidemiology it is accepted that the duration of different phases of disease is similar without treatment, I would argue that the duration of different phases would depend on other innate and environmental factors—including co-morbidities, nutrition status... acknowledgement of the limitation of the above assumption would be realistic. This is even more problematic in the assumption that the duration between diagnosis and treatment is 1 month! With the knowledge of health care systems in low and middle income countries, this is contra intuitive. I do understand that these assumptions were made due to lack of information from India and Uganda but lack of explicit reflection on how these assumptions may affect the results derived for the 2 contexts would provide the reader with a balanced perspective.

We assumed a uniform period of 2 months between symptom onset and treatment (allowing for delays by the patient and the medical care system). While this might be reasonable for high-income countries, it is probably too optimistic for middle and low income countries. While there are many local studies of related to specific cancers[4-6], we are not aware of any overall comparative assessment. In any case, a longer period of disability in this phase is likely to be offset by shorter pre-terminal and terminal phases, and the contributions of YLDs from these disease phases make up a very tiny proportion of the cancer-specific DALYs for lower income countries.

• A side question, one issued that the GBD study had to grapple with dealing with co-morbidities. Was this an issue in this analysis? If so, how was it handled?

We did not incorporate comorbidity in our analysis, and we have now included a discussion on this on page 19. Because our study assessed the burden i.e. disability due to cancer only, the disability due to co-existing disease did not come into consideration during the analysis of this paper. In a previous study where burden from multiple diseases were estimated, down-weighting the comorbidity[7] was done to avoid multiple counting of morbidities. If this were done, the vast majority of comorbidities will be less severe than cancer (e.g. arthritis, vision problems etc) and the comorbidity adjustments will not be very large. For severe comorbidities where the adjustment may be large, these will be very rare.

**Discussion:** Well written

**Limitations**

The issues raised in the methods section should be reflected on. The only identified limitations relate to the analysis of sequelae (both in the methods section and discussion). The authors need to reflect on the limitations of some of the assumptions made in the methods- generally. A distinct section on this would be useful.

*We have now added an extensive limitation section to reflect on the assumptions made in the Methods section (page 17-19).*

**Minor changes**

- Title: When reading the title, I expected to see a “framework”
We have now added the word methodological into the title which now reads “Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer”. We do think that our paper present the methodological steps in terms of the practical inputs required to calculate disability-adjusted life years in countries with widely-differing resource requirements.

- DALYs should be written in full the first time it is mentioned.

*We have now written DALYs in full when it was first mentioned.*

- In the Section on Proportion treated, the last sentence is too long, with many brackets inside brackets. This makes it difficult to understand.

*We have now split the sentence so the sentences are now shorter. We have as well removed the brackets so it is easier for readers to understand the sentences.*

- How do the results compare with the most recent GBD statistics of 2006? (especially for India and Uganda (where not recent studies eluded to in the discussion) have not been conducted).

*We have now added a graph to illustrate the similarities and differences to the earlier GBD statistics for the four represented countries in our study (see Figure 4, discussion on page 16). Country-specific results for DALYs are available for the discounted numbers and rates (standardized and crude). This figure illustrates the similarity of the estimates derived from both works, confirming the validity of our results.*
REFERENCES: