PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Investments in cancer research awarded to UK institutions and the global burden of cancer 2000-2013: a systematic analysis
AUTHORS	Maruthappu, Mahiben; Head, Michael; Zhou, Charlie; Gilbert, Barnabas; El-Harasis, Majd; Raine, Rosalind; Fitchett, Joseph; Atun, Rifat

VERSION 1 - REVIEW

REVIEWER	Jonathan Grant King's College London, UK
REVIEW RETURNED	02-Sep-2016

GENERAL COMMENTS	This is an important study that applies an approach developed to catalogue, describe and analyse infectious disease research funding through a 'bottom up' approach of collating grant information from funders and then qualitatively describing the funding data using various criteria. The study however is considerably undermined by the fact that it does not include CRUK funding (as, according to the authors, CRUK were unwilling to share this information). This actually makes it more important that the study is published, but it would be useful (and fair) to understand CRUK reasons for not making their data available. The paper would be significantly improved by a critical review of the approach taken to estimate and describe funding. Unlike infectious diseases, there have been other studies that have collated cancer funding data (i.e. Glover et al - cited 21 in paper; NB I am an author on this), HRCS data (which also describes funding characteristics) and more importantly the National Cancer Research Institute (NRCI) database. How do the data collected for this study compare against these estimates and what, if any, are the differences and how can they be explained. Crucially what does the current study add which these studies done. Related I am not sure the statement under the heading 'What is already known on this subject' is accurate. I would therefore recommend a revising the paper to address these two issues. Minor issues: what does 'unfunded' study actually me? Is it unsuccessful or a study that was complete with no funding? More exploration of the results of the BoD analysis would be interesting. I was surprised by the results i.e. prostate and testicular being 'over funded'

REVIEWER	Ashley Carter California State University Long Beach USA
REVIEW RETURNED	18-Sep-2016

GENERAL COMMENTS	Minor comments Page 2, lines 9-11: This statement is inaccurate, Carter, Hur & Delarosa (2015) did compare UK cancer funding across two recent time points, see first major point below. Page 3, line 32: "metrics" should be changed to "metric" Page 8, line 3: "the product of adding YLLs and YLDs" should be changed to "the sum of YLLS and YLDs" Page 15, line 26: "warded to UK institution" should be "awarded to UK institutions" Table 5 caption: "across mortality, DALYs, and YLDs" should be "across mortality, YLDs, and DALYs" to match the order within the table. Tables 1-4. The authors could add the sum of the percentages in their tables to show how this compares to 100% to give the readers a sense of how much data they are working with. They make reference to this in the text, but including it in the tables can be useful. Major comments 1. The authors should obtain the following three papers and incorporate them into the discussion: Burnet NG, Jefferies S.J.; Benson RJ; Hunt DP; Treasure FP. 2005. Years of life lost (YLL) from cancer is an important measure of population burden - and should be considered when allocating research funds. Br J Cancer. 92(2):241–55. Carter, A.J.R.; Nguyen, C.N. 2012. A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding. BMC Public Health, 12:526. DOI:10.1186/1471-2458-12-526. Carter, A.J.R.; Delarosa, B.; Hur, H. 2015. An analysis of discrepancies between United Kingdom cancer research funding and societal burden with a comparison to previous values and United States values. Health Research Policy and Systems 2015 13:62. DOI:10.1186/s12961-015-0050-7. All 3 papers analyze government funding and cancer burden as measured by YLLs, DALYs, mortalities, etc and discuss many of the same issues as the authors of this paper do. The 2005 and 2015 papers in particular deal with UK data; the 2015 paper making a comparison across two time points and discussing changes in cancer funding relative to burden over this time period. Some of the cancers identified as underfunded in those 3 papers match those

	identified by the authors; discussing how the new results match or differ from these previous ones is important. 2. Comparing one country's research effort to global burden may not be best analysis. Counties will tend to study diseases that affect their own citizens rather than others. The authors even specifically exclude studies that are global and not domestic UK (e.g., page 7, line 26) so their choice of global burden (as described on pages 7 and 8) instead of UK-specific burden for comparison seems strange. The burden metrics should be altered or a more complete justification of use of the global burden instead of UK-specific one should be included. 3. The compound metric used in Table 5 must be discussed or justified. It seems flawed as a true summary statistic to me for several reasons. First, by creating ranks instead of using the values, useful data is discarded. Second, averaging three different values that vary in their degree of inter-relatedness muddles the issue. Furthermore, why include mortality, YLD and DALYs but not YLL? Using Mortality, YLD and DALYs as metrics, but not YLL gives an incomplete picture. Also, since the DALY creates the potential for subjective bias (based on estimates of how bad a disability is) I would like to see YLL included or at a minimum a discussion of why it was omitted. To use the average to rank the values in the table seems fine, but I hesitate at placing a real objective meaning on the compound metric obtained from averaging these very different concepts. 4. An additional approach that the authors should consider (consider this a non-mandatory recommendation) is to perform a series of rank-correlations for the funding vs their three metrics (and YLL, see above). The correlation coefficients would indicate the match or mismatch between funding and each metric and create a useful point for discussion (e.g., page 13, lines 19-21).

VERSION 1 – AUTHOR RESPONSE

Jonathan Grant:
Minor issues:
What does 'unfunded' study actually me? Is it unsuccessful or a study that was complete with no funding?
More exploration of the results of the BoD analysis would be interesting. I was surprised by the results i.e. prostate and testicular being 'over funded'

Authors' response: We have clarified the meaning of unfunded study in our manuscript. Potential explanations as to why certain cancers are relatively well funded compared to others would be purely speculative and so we have not given a lot of discussion to this. However we do mention that the sex-specific cancers (breast, prostate, testicular, ovarian) may benefit from successful and influential awareness campaigns. Mesothelioma, on the other hand, is such a rare disease that any funding towards it is likely to be distorted by its disproportionately low disease burden in comparison to other cancers.

Ashley Carter: Page 2, lines 9-11:
This statement is inaccurate, Carter, Hur & Delarosa (2015) did compare UK cancer funding across two recent time points, see first major point below.

Page 3, line 32:
"metrics" should be changed to "metric"

Page 8, line 3:
"the product of adding YLLs and YLDs" should be changed to "the sum of YLLS and YLDs"

Page 15, line 26:
"warded to UK institution" should be "awarded to UK institutions"

Table 5 caption:
"across mortality, DALYs, and YLDs" should be "across mortality, YLDs, and DALYs" to match the order within the table.

Tables 1-4.
The authors could add the sum of the percentages in their tables to show how this compares to 100% to give the readers a sense of how much data they are working with. They make reference to this in the text, but including it in the tables can be useful.

Authors' response: All these amendments have been made

Ashley Carter: 1. The authors should obtain the following three papers and incorporate them into the discussion:

Burnet NG, Jefferies S.J.; Benson RJ; Hunt DP; Treasure FP. 2005. Years of life lost (YLL) from cancer is an important measure of population burden - and should be considered when allocating research funds. Br J Cancer. 92(2):241–55.
Carter, A.J.R.; Nguyen, C.N. 2012. A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding. BMC Public Health, 12:526. DOI:10.1186/1471-2458-12-526.
Carter, A.J.R.; Delarosa, B.; Hur, H. 2015. An analysis of discrepancies between United Kingdom cancer research funding and societal burden with a comparison to previous values and United States values. Health Research Policy and Systems 2015 13:62. DOI:10.1186/s12961-015-0050-7.

All 3 papers analyze government funding and cancer burden as measured by YLLs, DALYs, mortalities, etc and discuss many of the same issues as the authors of this paper do. The 2005 and 2015 papers in particular deal with UK data; the 2015 paper making a comparison across two time points and discussing changes in cancer funding relative to burden over this time period. Some of the cancers identified as underfunded in those 3 papers match those identified by the authors; discussing how the new results match or differ from these previous ones is important.

Authors' response: We agree with the author and we have amended the discussion to reconcile our findings with those previously reported in the scientific literature.

Ashley Carter: 2. Comparing one country's research effort to global burden may not be best analysis. Counties will tend to study diseases that affect their own citizens rather than others. The authors even specifically exclude studies that are global and not domestic UK (e.g., page 7, line 26) so their choice of global burden (as described on pages 7 and 8) instead of UK-specific burden for comparison seems strange. The burden metrics should be altered or a more complete justification of use of the global burden instead of UK-specific one should be included.

Authors' response: We appreciate the reviewer’s comments and this was a key consideration at the

design phase of this study. However, the amendments that the reviewer is suggesting are extensive, would essentially change the entire content and message of the manuscript. Due to increasing globalization, the emergence of non-communicable disease burden in resource poor-settings, the internationalization of healthcare, the flow of people across national borders and the role of the UK as an international center of biomedical research, we believe that approach is justified. However, the comparison suggested by the reviewer is a meaningful one and something that we plan to address.

Ashley Carter: 3. The compound metric used in Table 5 must be discussed or justified. It seems flawed as a true summary statistic to me for several reasons. First, by creating ranks instead of using the values, useful data is discarded. Second, averaging three different values that vary in their degree of inter-relatedness muddles the issue. Furthermore, why include mortality, YLD and DALYs but not YLL? Using Mortality, YLD and DALYs as metrics, but not YLL gives an incomplete picture. Also, since the DALY creates the potential for subjective bias (based on estimates of how bad a disability is) I would like to see YLL included or at a minimum a discussion of why it was omitted. To use the average to rank the values in the table seems fine, but I hesitate at placing a real objective meaning on the compound metric obtained from averaging these very different concepts.

Authors' response: We have captured mortality burden and life burden in our selection of global mortality, YLD and DALY. The omission of YLLs is a small limitation of our study (potentially under-representing the disease burden of cancers that disproportionately affect the young and which are associated with poor survival prognosis). We have amended our discussion to include this limitation. However, we would expect any additional information offered by YLL analysis to be predominantly captured by use of DALYs and YLDs. Our aim with Table 5 is to provide a general indicator of relative cancer research funding; there is a pragmatic component to putting this analysis together, and there much also be pragmatism in interpretation of the results and what can be reasonably inferred from them. We feel that it adds useful information that is not captured in the previous tables.

Ashley Carter: 4. An additional approach that the authors should consider (consider this a non-mandatory recommendation) is to perform a series of rank-correlations for the funding vs their three metrics (and YLL, see above). The correlation coefficients would indicate the match or mismatch between funding and each metric and create a useful point for discussion (e.g., page 13, lines 19-21).

Authors' response: Thank you for this recommendation. In the analysis of our data, we have already generated metrics that provide £/death, £/YLD and £/DALY which we present in our new supplementary documents. We do not think that rank-correlations would provide significant additional rigor to our existing calculations.

VERSION 2 – REVIEW

REVIEWER	Jonathan Grant King's College London, UK
REVIEW RETURNED	04-Nov-2016

GENERAL COMMENTS	I don't think the authors have addressed 2 or my 3 major concerns and I would like to see them addressed as they are important. The first is to do with the non-discolusre of CRUK funding. This is a major caveat to the study but raises serious issues of data openness and accountability that must be raised in the discussion. The have put in a wimp statement saying this is CRUK policy. If this is the case it is simply not good enough. If we are to have an evidence based science policy then data of this sort should be made available. The authors must make this point strongly otherwise there is no value to the paper (given CRUK funding is excluded).

	The second is to do with previous estimates of cancer R&D funding. As noted in my earlier comments there are other studies. it is important that they compare and contrast their findings with these other studies and if the cannot (for methodological reasons) they should explain why

VERSION 2 – AUTHOR RESPONSE

Reviewer's comments: I don't think the authors have addressed 2 or my 3 major concerns and I would like to see them addressed as they are important.

The first is to do with the non-disclosure of CRUK funding. This is a major caveat to the study but raises serious issues of data openness and accountability that must be raised in the discussion. The have put in a wimp statement saying this is CRUK policy. If this is the case it is simply not good enough. If we are to have an evidence based science policy then data of this sort should be made available. The authors must make this point strongly otherwise there is no value to the paper (given CRUK funding is excluded).

Authors' response: We agree with the reviewer's concerns and we have sought to address it as follows:
1. We have cited two papers calling for increased data transparency from funding agencies and the importance of such data towards policy making (Fitchett et al, Davies et al).
2. We further highlight how CRUK's decision not to share its disaggregated funding data is in direct conflict with its publically expressed stance on data sharing (Teperek) and how this contrasts with the position of over 200 other high-profile research funders (Fitchett et al)
3. We have included a section in the conclusion strongly urging CRUK to share their funding data.

Reviewer's comments: The second is to do with previous estimates of cancer R&D funding. As noted in my earlier comments there are other studies. It is important that they compare and contrast their findings with these other studies and if they cannot (for methodological reasons) they should explain why

Authors' response:
We have presented previous studies investigating cancer research funding (Burnett et al, Carter et al) and we highlight the consistency of our findings to those presented in the literature. Potential explanations are offered as to why our findings may differ slightly from those previously published. We further sought to expand upon how our study contributes towards the established literature.

VERSION 3 – REVIEW

REVIEWER	Jonathan Grant King's College London
REVIEW RETURNED	18-Dec-2016

GENERAL COMMENTS	The authors have now addressed my concerns and I am happy to support this paper for publication.