Author’s response to reviews

Title: Literature review of the burden of prostate cancer in Germany, France, the United Kingdom and Canada

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Author’s response to reviews:

Firstly, we’d like to thank the reviewer for their careful and objective review of our manuscript. We have responded to the reviewers concerns below and have made the necessary edits and updates to the manuscript (for clarity the changes to the manuscript have been made in blue text). We hope that we’ve satisfactorily addressed the reviewers concerns; however, if there are any areas that need further clarity of detail we would be happy to make any additional changes deemed necessary.

Additionally, we have also updated the manuscript to include all declarations stipulated in the editorial comments.

Reviewer reports:
John Yaxley (Reviewer 1): This manuscript aims to characterise the clinical, economic and humanistic burden of disease associated with prostate from France, Germany, the UK and Canada

As per the BMC Urology guidelines, I would separate the results from a discussion on the results. In this manuscript the results and discussion are together in the results section. Also, try to avoid discussing incidence outcomes in the same paragraph as discussion on mortality outcomes.
Abstract: acceptable

Introduction:

Add that the USPSTF has suspended its recommendation against PSA screening, particularly following the NEJM publication in 2016 re-evaluating the contamination of the control arm.

We have updated the introduction to include the new USPSTF recommendations. This section now states:

“In the United States, in 2008 the Preventative Services Task Force (USPSTF) recommended against routine screening due to its psychological harms and uncertainty around its clinical benefits. However, the USPSTF recently updated its recommendations for men aged 55–69 years, stating that men should be informed of the potential benefits and harms of PSA screening and that the final decision should rest with the individual.”

I would suggest a comment on the ProtecT randomised trial, with a <2% prostate cancer specific mortality over 10 years in a predominately (~75%) low risk cohort. This would support the potential for 'over treatment' in the low risk cohort. Thus increased active surveillance / monitoring could potentially decrease the economic burden of prostate cancer treatment. However the ProtecT study also identifies 20% of men in the active monitoring arm that develop clinical progression into advanced disease, ureteric obstruction, urine retention and requirement for ADT. This progression impacts on QOL and economic burden in the active monitoring cohort. I would also explain that physicians are aware of 'over treatment' and add a sentence showing the increased uptake of active surveillance over the last decade in the 4 countries evaluated to highlight the attempt to decrease over treatment of low risk prostate cancer.

Firstly, we’d like to thank the reviewer for raising the issue of the findings of the ProtecT trial, which represents a valuable addition to the manuscript. In line with recommendations, we have added information on outcomes from the ProtecT trial to the introduction (page 5, paragraph 3).

We have also updated page 5, paragraph 3 of the introduction to incorporate the reviewer’s recommendation to state that physicians are aware of over-treatment and the increased use of active surveillance likely reflects efforts to reduce the over-treatment of low-risk prostate cancer. Specifically, the text now states:
“The phenomenon of over-treatment is becoming increasingly recognized by physicians and consequently the strategies of watchful waiting and active surveillance are now recommended in several guidelines for men with low risk/early stage prostate cancer. Moreover, an increased uptake in active surveillance in recent years likely reflects efforts to reduce the over-treatment of low risk prostate cancer.”

When discussing the potential complication of 'curative treatments' the complications of radiotherapy treatments should also be discussed, rather than just discussing radical prostatectomy outcomes.

We have updated the text (page 5, paragraph 2) to include complications of radiotherapy treatments (painful urination, urinary incontinence, urethral stricture, rectal bleeding and/or leaking, erectile dysfunction and lymphedema)

In contemporary urological practice MRI scans are also increasingly used as a triage tool in evaluation of an elevated PSA, in an attempt to decrease the number of men proceeding with a prostate biopsy as primary evaluation of an elevated screening PSA test. The decreased number of prostate biopsies and decreased number of men diagnosed with low risk prostate cancer from random biopsies may also have the potential to decrease economic burden. You could discuss this in the introduction, or alternatively in the concluding remarks after discussing genomic profiling.

We have updated the introduction section (paragraph 2 page 6 and beginning of page 7) to include reference to the increasing role of MRI in guiding biopsies to improve the detection of clinically significant tumors as well as including reference to the emerging role of MRI in active surveillance and detection of local recurrence following treatment. We have also included reference to increased use of MRI contributing to increasing economic burden in the Discussion section of the manuscript.

Methods: Acceptable and limited to publications after 2006
Results

Again, you need to outline the results as related to the tables. Discussion of these results should be in a separate section under 'Discussion'.

We have restructured the manuscript and created a separate discussion section to clearly delineate results from the discussion of the context of the results.

Although the methods states that searches were limited to publications after 2006, only 8 publications relate to incidence data after 2006, with the latest incidence data from the year 2011. This gives an impression the manuscript does not relate to contemporary outcomes. In Germany and France only 1 manuscript relates to incidence per 100,000 after 2006.

We have added a paragraph to the Discussion section of the manuscript to state that this is a key limitation of the manuscript.

The paragraph on ethnicity should be in a discussion section, not results.

We have restructured both the results and discussion section and this paragraph has been moved to the discussion section.

The incidence of PC can also relate to the selection of population groups (west of Scotland) and also the quality / methods of data collection. Where incidence per 100,000 is vastly different, a comment on the possible bias of group or data collection methods should be discussed.

We’d like to thank the reviewer for this valuable comment and have added a brief discussion of the potential for incidence data to be influenced by the quality/methods of data collection and the population groups included in the study.

When discussing mortality from prostate cancer it is well known that at least 15-20 years of follow up is required for enough prostate cancer specific deaths to occur to influence outcome data. When discussing the six studies on 5-year relative survival rates, the stage shift from PSA
screening is the most likely cause of improved 5 year outcomes, combined with improving treatment options of advanced / metastatic disease. In table 2 on mortality there is only 4 publications with mortality outcomes specifically after 2006, again giving an impression that this data is not relating to contemporary urological practice. I would specifically address the outcomes of these publications compared to earlier data.

In line with the comment above as well as other comments, we have updated the Discussion section to acknowledge that some of the older mortality data included in the review may not accurately reflect current mortality rates. Specifically the following text has been added:

“A further limitation is that in terms of 5-year relative survival data included in the review, the most recent data are from 2010, which again may not accurately reflect the current situation in routine clinical practice. Allied to this, in the area of oncology long-term follow-up (typically 15–20 years) is required to fully investigate and elucidate the underlying mechanisms for changes in mortality rates. Only a small number of studies included in the review were conducted over time horizons of >15 years.”

The first paragraph of the Bray et al paper discussing PC incidence should be discussed in the paragraph on incidence, not in between paragraphs on mortality data. This will decrease confusion and maintain continuity of discussion. The mortality section of the Bray et al can remain in the mortality discussion section.

In line with the reviewer’s suggestion we have moved the paragraph from the Bray et al. paper to the incidence section of the results (page 9 paragraph 1).

The final paragraph on data from 1975-2004 is interesting, but again gives the reader a sense of lack of relevance to contemporary urological practice after 2006. The number of men that undergo radical prostatectomy in in the US and UK has changed from 2004. I would suggest that this paragraph is deleted, or delete the last sentence.

We have deleted the sentence “For example, in the US approximately 30% of men with prostate cancer undergo radical prostatectomy, whereas in the UK in 2004 the corresponding figure was 10%”
In line with the reviewer’s suggestion. We have also added the following sentence to add that there have been considerable advances in the treatment of prostate cancer since 2004, which will likely have influenced mortality rates in both the US and UK.

“However, it should also be noted that there have been considerable advances in the treatment of prostate cancer since 2004, which may have influenced mortality rates in both the UK and US.”

Economic Burden of PC

This is a complex area with costs of RP, radiotherapy, advanced disease and metastatic disease evolving with new technologies. New diagnostic tests such as 3T MRI / genomic tests, PET PSMA scans, robot prostatectomy costs, brachytherapy technology, increasing use of chemotherapy agents earlier in metastatic hormone naive disease and more anti-androgens available, all add to the cost burden. This could be briefly outlined in the discussion section on economic burden.

In line with the reviewer’s suggestion we have updated the Discussion to add some text on the fact that the date of publication of many of the included economic articles may not adequately reflect the costs associated with the uptake of the most recently introduced diagnostic approaches, treatments and surgical approaches. Specifically, the following text has been added (page 17).

“Factors contributing to the increasing economic burden include increasing incidence, advances in treatment and advances in diagnostic and monitoring technologies such as the increased use of MRI and the introduction of genomic profiling tools. However, it should be noted that some of the cost data included in the current review may not adequately capture the direct costs, or savings, associated with the most recent advances in the treatment of prostate cancer. For example, increased use of robot-assisted radical prostatectomy is associated with increased surgical costs relative to open or laparoscopic radical prostatectomy. Additionally, increasing use of advances such as prostate-specific membrane antigen based PET or CT imaging and 3T MRI in the diagnosis of prostate cancer are also likely to have influenced the overall economic burden of disease.”

Quality of life

I agree the scope of the literature review limits the options to discuss QOL, otherwise satisfactory discussion here.

I hope the above suggestions will be of benefit in revision of your manuscript.