Author's response to reviews

Title: The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers.

Authors:

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Version: 4 Date: 29 May 2015

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

RE: MS: 7655004815910365 - The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers.

Thank you for the positive comments on our manuscript. We have made a point-by-point response to the Reviewers’ comments as outlined in the following pages, using blue font to indicate our reply. In the revised manuscript we have indicated the in-text changes using blue font (for your convenience).

We hope that these revisions are satisfactory and that our manuscript is now acceptable for publication. Should you require any further information, please do not hesitate to contact us (k.rogers@qub.ac.uk).

Yours sincerely,

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Dr. K. Rogers and Ms H Cavanagh.

Encl.
Reviewer's report – Authors’ Response to Reviewer's Report (author comments in blue font for your convenience)

Title: The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers.
Version: 1 Date: 6 March 2015
Reviewer: Wojciech Klucznik

Reviewer's report:
Comments to author:
This is a well presented manuscript, showing a wide range of studies on BRCA1/2 mutations carriers and its associations with cancers of prostate, pancreas and stomach. Majority of clinicians are mostly focused on breast and ovarian cancers while facing families with BRCA1/2 mutations. Therefore, this review might be a very valuable set of information about prostate, pancreas and stomach cancers showing not only the association with the risk but also frequency of those cancers among families and stating that BRCA2 gene is associated with poor survival. These information might be valuable for assessing specific surveillance program for carriers or set a more effective treatment.
Manuscript is well divided into chapters which make it easily to comprehend. Developing standard procedures for cancer risk assessment is of a broad interest among geneticists where such procedures are clearly stated for females but it is not well reasoned for males especially for carriers with BRCA1/2. Thank you for your positive summary of the article.

- Major Compulsory Revisions
  No major issues were found.
- Minor Essential Revisions
  There are too many repeats (mostly mentioning about BRCA1/2 and prostate, pancreatic and stomach) in the abstract, while the paper represent a good standard of writing, try to omit those repeats so the paper would more eye-catchy. The abstract is a very important part of the manuscript and should represent the most valuable information in the paper so the reader could consider it as worth reading. Agreed! Thank you for pointing this out. We have reworded parts of the abstract to make it sound better – we hope you agree that it is less repetitive now?
- Discretionary Revisions
  The author should give some information or his own opinion about the surveillance programs. The frequencies of BRCA1/2 mutations in specific ethnicities might be of interest so it will give information about which mutation is studied and which are mostly frequent. It might help in diagnostic procedures in which cases we should do the sequencing of entire genes. Agreed. We have added a section on screening/surveillance near the end of the manuscript (on page 17). We had a version of this in our original draft but removed it prior to our original submission to conform to the recommended word limit.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: No conflict of interest
Authors’ Response to Reviewer’s Report (author comments in blue font for your convenience)

1061892535119615 – Reviewers comment, Dr Talseth-Palmer:
This review discuss the role of BRCA1/2 in cancer development in cancers other than breast and ovarian. The review is informative and contains important information for people interested in genetic associations in inherited cancer. An article of importance to its field. Thank you for your positive summary of the article.

Major Compulsory Revisions
No major compulsory revisions required.

Minor Essential Revisions
The review needs to be updated to include references from 2013/2014/2015 and especially but not limited to: Olmos, D (Clin Adv Hemat Onc, 2013), Castro, E (Eur Urol, 2014), Alanee, SR (Front BioSci, 2014), Becker, AE (World J Gastroent, 2014), Golan, T (Br J Can, 2014), Laitman, Y (Br Can Res Tr, 2015), Mersch J, Cancer 2015) and Vyas, O (Antican Drugs, 2015). Thank you very much for suggesting these recent relevant articles. We attempted to source all of the above listed and have included some in the revised manuscript. However we were unable to gain full-text access to some papers and so have not included any in the revised manuscript which we were unable to access and read in full.

Introduction – 2nd paragraph: ..... area of the body where the gene was situated. Rephrase, as the gene is found in all areas of the body. Done, inserted the word “mutated” before “gene” to make the sentence clearer.

Introduction – 3rd paragraph: You have mentioned that BRCA2 gene is on chromosome 13, maybe also state that BRCA1 is on chromosome 17. Done – thank you for the suggestion; it was in our original draft manuscript but we removed it prior to our original submission to conform to the recommended word limit.

Review – all through: A lot of sentences that needs to be referenced we agree that some of the sentences listed needed references or the reference citation needed to be moved. However in some places we have not adjusted the referencing as suggested because of either [1] or [2] described below:
[1] we feel that the inclusion of references where the Reviewer has suggested would interfere with the readability of the article and disrupt the flow of the article; or
[2] Some of the points listed below are our own hypotheses and opinions, therefore we feel it would be inappropriate to reference these points.

We have addressed each suggestion below.

- 2nd paragraph:
  o Since the advancement, considerable research..... [Ref]. this is our own observation so we have not referenced it.
  o Familial aggregation of prostate cancer has been described...... [Ref] done #13
  o To date, many have reported on the association of both BRCA1/2 mutations [Ref] and some findings..... [12,13] no change, for reason [1] above
  - 3rd paragraph:
    o Some studies also suggest that men with prostate cancer who...... [Ref] no – as the reference is cited in the following phrase “In the study by Agaillu...” to include it as suggested here would interrupt the flow of text [reason [2] above]
  - 10th paragraph:
    o Environmental and genetic factors have been proposed as causes.... [Ref] we have revised and merged this sentence with the following sentence and incorporated a ref #29
    o The genetic factor of particular importance is the BRCA2 gene [Ref] done, as above.
  - 12th paragraph:
    o It is clear that BRCA1/2 mutations are evident in many familial breas-pancreas families [Ref] no change, for reason [1] above and the carriers of the BRCA2 mutation have an increased...... [Ref] done#33
    o Perhaps, differences in population...... [Ref] no change, for reason [2] above
    o Furthermore, the use of different analysis models..... [Ref] no change, for reason [2] above
  - 21st paragraph:
    o BRCA2 mutations were identified among 23.5% in families where stomach cancer occurred [Ref] done. Merged with previous sentence where ref # 41 is included.

Review – 3rd paragraph: “Several studies indicate that male carriers of BRCA2 are at an increased risk of developing prostate cancer [15]”. Cannot say several studies and only reference one. Added ref #13

Review – 8th paragraph: “It would seem reasonable to suggest that social class status could have possible implication for cancer survival.....”. Please explain how you got to this conclusion. Nothing you have written would suggest that. This sentence has been removed as it does not add anything beneficial to the discussion.

Review – 9th paragraph: “This suggests BRCA2 is a high risk prostate cancer susceptibility gene.” Can you make
this conclusion from the previous sentence? This sentence has been reworded.
Review – 15th paragraph: Move the sentence in brackets to behind “.... aged 35 years presented significant standard incidence ratios (ratio that allows comparison of incidence rates among different populations) for pancreatic cancers.” Done - reworded
Review – 17th paragraph: “Thus, this further suggest that BRCA1/2 mutations can be attributed to early-onset breast cancer [34]”. Add if you find that it correct: ...... and prostate (?) but not necessarily early-onset pancreatic cancer [Ref]. no change here.
Review – 19th paragraph: Add [38] behind second last sentence. Done
Review – 20th paragraph: “The relative risk of stomach cancer was significantly increased and was reported to be 2.40-fold for.......”. Please specify which group of patients you are referring to – mutation positive or negative? Done – added “among the BRCA2 mutation positive cohort”
Review – 21st paragraph: “It has been suggested that the frequency of stomach cancer appears greater among Polish families with BRCA2 mutations [38].” Can this also be due to more Jewish people in this sample cohort? Please discuss. Done – added “but again this could be due to a higher proportion of participants of Jewish decent”
Review – 22nd paragraph: “Findings showed that 23 families with breast, ovarian...” add ref [24] to the end of sentence. Done – (N.B. this is the same ref but now ref#26 due to new refs added)
Review – 23rd paragraph: “Therefore, it is possible that the risk of stomach cancer in this study may be overestimated.” Add: ... or underestimated. Not all relatives have all cancer info for their families. Done – added “or underestimated.”
Review – 24th paragraph: Change second sentence to: The association of BRCA1/2 gene mutations with cancer of the prostate, pancreas and stomach has been demonstrated in a number of studies as discussed in this review. Add another reference to sentence three as [18] only refer to BRCA2 and you say “... mutations in the BRCA1/2 genes.” Done
Conclusion – The conclusion needs to be rewritten to include the fact that it looks like BRCA2 is the gene that increases the risk of the prostate, pancreas and stomach cancers the most (that is my impression after reading the review) and that it influences the risk, survival, gender and early onset. The conclusion as it is, is very broad and does not summarise what the review has stated. Done – as suggested added another paragraph at the end to highlight impact of BRCA2
Authors’ Response to Reviewer’s Report (author comments in blue font for your convenience)

Reviewer's report
Title: The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers.
Version: 1 Date: 30 March 2015
Reviewer: Elizabeth Bancroft

Reviewer's report:
Major Compulsory Revisions
1. Does it address an important or timely issue?
a) This is an issue that has been addressed by others, however it remains an interesting topic because there is still not consensus between studies. However there are several failings in this review. First and foremost the literature reviewed is old, and several notable studies are missing. Looking at the reference list, excluding web references out of the 40 references cited, there is one article from 2012, one from 2010 and the majority are much older. For this article to be considered, a thorough review of the literature over the last 5 years should be conducted. Recent notable papers on this very topic are missing. In addition there have been several key publications about the risk of prostate cancer and pancreatic cancer from large international consortia. These should be included. References have been revised and updated throughout the manuscript.
b) It is not clear how these cancers were chosen as the focus of this review. In places it sounds like it was to be a review of the risks for men, but this is not the case. The review states that it is also to focus on screening but this has not been included. There is a brief mention of prostate screening but this does not address any of the complexities of this area of debate or include any mention of the IMPACT study which is ongoing and aiming to address this very question. These issues have been addressed. The review does not claim to be a focussed on males however since prostate cancer will inevitably be male specific it is inevitable that aspects of the discussion are male focussed. Screening has been included the revisions. It was in the original manuscript but removed due to word limit constraints. The IMPACT study was referred to in the original submitted version of the manuscript.

2. Is it well reasoned?
a) The authors have not described the methods used to conduct the review, other than stating “the most relevant available literature” – it would be helpful for the reader to understand how the papers reviewed were selected, what the inclusion criteria were, the time frames for the searches and the key words used for the searches. Also an explanation for why these three cancers were chosen out of all the cancers that are associated with these genes? What was the rationale for undertaking this review? Word limit constraints limit the inclusion of many aspects of the review. We felt that inclusion of methodology detail was not the best use of words therefore we chose to omit such detail so that we could include more pertinent discussion namely the screening debate.
b) The abstract states the aim was to examine the association of BRCA1/2 germline gene mutations with cancers other than breast or ovarian – this is not the case, it has been limited to three cancers. The abstract does not state a discussion of ALL cancers – additional cancers were included in the study but have been omitted from the manuscript due to word limit constraints, the three included were chosen since they were the cancers most commonly associated with mutations in these genes.

c) The authors have largely considered BRCA1 and BRCA2 to be the same. Better attempts to separate the two genes should be made, particularly in regard to pancreatic and prostate cancer where the evidence for the role of BRCA2 is much less controversial compared with BRCA1. BRCA1 and BRCA2 are often considered together when discussing their mutations, studies referring to one or both were examined as part of this review.
d) The review is more of a narrative as written rather than offering a critical viewpoint. Study limitations are rarely drawn on. In particular, in discussing stomach cancer the majority of papers acknowledge that they are using unverified series with self-reported cases of cancers. Stomach cancer is often mistaken for gynaecological cancers and this limitation should be mentioned. We feel this would not add to the paper and given that we are examining non-breast or ovarian cancers referring to gynaecological cancers may only serve to confuse the reader.

e) A table summarising the key points of all of the papers would be helpful for the reader. This would allow some of the text describing study populations could be taken out of the text. We feel this would not add to the paper.

f) In the prostate cancer survival section – last sentence of para 1 – what does this have to do with the review? Either expand or remove. Likewise the second to last sentence of para 2 – how has the previous sentence informed this statement? No other Reviewer agreed with this and since the paper is reviewing the impact of BRCA1/2 mutations on these cancers we feel a comment in relation to the survival rates is relevant.

g) Be careful how you review papers that are looking at cohorts of BRCA1/2 carriers vs those looking at disease cohorts and reporting the incidence of mutations, these are not always directly comparable. Noted.

h) The last section before the conclusion (impact of BRCA1/2 mutations in other associated cancers). Either this should be fully reviewed and the whole paper changed accordingly or removed as this is not what is stated the review aimed to do. This has been revised in response to feedback from the other Reviewers. We feel that it does not contradict the abstract and its inclusion is important as it acknowledges the relationship between BRCA1/2 mutations and other cancers but due to word constraints we were unable to include extensive discussion of in this manuscript.

i) Conclusion – needs to be completely re-written. It is confused and disjointed. State what the review has found, what it adds to the evidence and suggest what implications this has for practice if targeting a clinic journal. Revised.

3. Is it relatively balanced, or does it make plain where the author’s opinions might not represent the field as a whole?

There is no obvious author bias, but in the absence of a thorough and comprehensive review it is difficult to fully assess.

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?

There are no figures or tables, but as suggested above a summary table would be helpful.

5. Is the standard of writing acceptable?

a) The introduction is a little too simplistic for this journals audience and the word count could be cut here. The background to the discovery of BRCA1/2 is not necessary to this audience. We feel it would be inappropriate to remove all background information – the information included is brief and relevant.

b) Make sure that all statements are appropriately referenced so that it is clear where the data reported has come from.

c) A background to each of the cancers would be beneficial at the start of each cancer section. We have included relevant information such as incidence, risk and/or survival etc. Detailed pathophysiology is not as relevant.

d) The manuscript is repetitive in places and should be revised to remove repetition. Parts of the manuscript have been revised as indicated in blue font.

e) Introduction, paragraph 4 – reference 10 does not relate to the Evans et al paper cited here – please double-check all references. This is the correct reference although Evans is the second author – it has just been incorrectly cited. Correction made. (It is now Ref 11 due to insertion of new refs.)

f) The manuscript often uses the statement “recent years”, “recent times”, “recently found” when referring to literature dating back over 10 years. This
needs to be corrected. Agreed that is some occurrences this is unnecessary and has been corrected.

g) In discussing the “founder” mutations the population needs to be defined and explained. Presumably the Ashkenazi Jewish population.
h) Pancreatic cancer – paragraph 4 – too much detail about one study (Axilbund et al) – this should be removed. Paragraph 6 – last sentence is about breast cancer, this should be removed as it is not the focus of this review. Paragraph 8 – last sentence, again this review is not about breast cancer – the evidence for a link of BRCA1/2 with breast cancer is undisputed! Agreed. Superfluous detail removed.
i) Stomach cancer second paragraph - last sentence should be removed. Now that the manuscript includes some discussion on screening we feel this statement should remain.
j) Stomach cancer 5th paragraph last sentence – where is the evidence to support this claim? Author postulation/hypothesis

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests