Author's response to reviews

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

Authors:

Helen Cavanagh (helen21987@hotmail.com)
Katherine MA Rogers (k.rogers@qub.ac.uk)

Version: 3  Date: 1 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 Klu¿niak

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 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
- 6th 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] 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