Author’s response to reviews

Title: Increased Breast Cancer Risk in Women with Neurofibromatosis Type 1: A Meta-analysis and Systematic Review of the Literature

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Increased Breast Cancer Risk in Women with Neurofibromatosis Type 1: A Meta-analysis and Systematic Review of the Literature
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Reviewers’ Comments and Response Summary

Reviewer #1:
1 – “The paper is a meta-analysis of literature data on the incidence of breast cancer in patients with NF1. This analysis concerns an important problem, rarely discussed. The methodology is correct. The conclusions are balanced. I recommend this work for publication in its current form.”

Response: Thank you very much for your review and support.
Reviewer #2:
1 – “The authors have undertaken a meta-analysis of studies assessing breast cancer incidence pathology and survival. They have identified only 4 studies that fulfilled their preset criteria. The study is well executed and provides a useful overview. It is a shame that their timeline has missed the important large Finnish population based study -Uusitalo et al. Why is it so long since the timeline?”

Response: Thank you very much for your review and appreciate your response. In the completion of the manuscript, we unfortunately experienced some unexpected delays. We agree that the large Finnish population-based study by Uusitalo et al.is important. However, even if included in our timeline for inclusion, this study does not meet criteria for inclusion into our analysis as it does not present standardized incidence ratio, relative risk, odds ratios, or hazard ratio estimates or sufficient data with which to calculate these for the risk of breast cancer in women < 50 years of age or ≥ 50 years of age. Therefore, the importance of this study was included in the discussion section of the manuscript.

Pg. 14: A recently published study not included in the meta-analysis of this manuscript was conducted by Uusitalo et al. to evaluate the cancer incidence and mortality in a population based cohort of 1,404 (737 women) Finnish patients with NF1. [11] In this study, thirty-one (4.2%) women developed breast cancer and the risk of breast cancer was found to be significantly higher in NF1 patients younger than 40 years of age compared to this age group in the general population; SIR = 11.1 (95% CI: 5.6-19.5). [11] Additionally, Uusitalo et al. demonstrated that women with NF1 have a five-fold increased risk of breast cancer mortality compared to the general population with a SMR of 5.2 (95% CI: 2.4- 9.9) and found that when breast cancer survival was analyzed alone, 5-year survival was poorer in patients with NF1 compared with those without NF1 (67.9% vs. 87.8%, respectively). [11]

2 – “Comparisons were made with the general population using the SEER database. This needs to be at least controlled for year at diagnosis. It should also be acknowledged that survival in SEER is better than in some countries of origin of cases such as the UK.”

Response: We apologize if there was any misunderstanding, but the SEER data used was controlled for both age at diagnosis and year at diagnosis. This information is included in the methods section on Pg. 10. The discrepancies in breast cancer survival between the different countries included in the NF1 cohort compared SEER survival reports was acknowledged in the discussion section on Pg. 12.

Pg. 10: The relative survival of the female NF1 patients with breast cancer identified in this study was compared to the general population using the SEER database controlling for age and year at diagnosis for each patient (Figure 3).

Pg. 12: These findings suggest that there is a high incidence of breast cancer in NF1 women younger than 50 years of age and that these women tend to present with more advanced disease and possibly experienced an increased breast cancer related mortality. However, it is important to note that true comparison with SEER database is difficult with this cohort of patients as these patients originated from 23 different countries and the survival reported in the USA SEER database may be better than in some other countries included in this cohort.

3 – “A recently published study not included in the meta-analysis of this manuscript was conducted by Uusitalo et al. to evaluate the cancer incidence and mortality in a population-based cohort of 1,404 (737
women) Finnish patients with NF1. -it is a shame this study was not included we are now over 3 years after the end date of their PubMed search. This is quite a long time to get a meta-analysis conducted and reviewed for publication. The Uusitalo study is clearly important and would boost he numbers substantially.”

Response: In the completion of the manuscript, we unfortunately experienced some unexpected delays. Prior to submission to this journal, a review of the literature was conducted and the only recent manuscript published since the completion of the meta-analysis systematic literature review identified to be potentially included in this study was by Uusitalo et al. However, for the reasons discussed above it did not meet criteria for inclusion in this analysis.

4 – “The NF1 gene and (BRAC1) gene are both on chromosome 17...’ Misspelling of BRCA1”

Response: Error has been corrected.

5 – “However, pathogenic variants in the NF1 gene were not associated with increased risks of breast cancer. [91]’ Please see recent review of panel testing (https://www.ncbi.nlm.nih.gov/pubmed/30510771) it is highly likely that NF1 is selected out of testing due to known diagnosis or other factors.”

Response: Thank you for pointing out this important and interesting review. This review was published after our manuscript was submitted to Hereditary Cancer in Clinical Practice, but it has now been included in the discussion section of the manuscript.

Pg. 17-18: But, pathogenic variants in the NF1 gene were not associated with increased risks of breast cancer. [91] Several other studies assessing the risk of breast cancer with multi-gene panels have also failed to demonstrate an association with NF1 pathogenic variants and an increased risks of breast cancer. [92-94] However, Evans et al. warn about the potential pitfalls of using commercial multi-gene panels to confirm syndromic associations with cancers, in particularly NF1 and breast cancer. [95] Their review discussed two main reasons why pathogenic variants in the NF1 gene may have not been associated with an increased risks of breast cancer; 1) it is likely that patients with NF1 are selected out of testing due to their know diagnosis or other socioeconomic factors and 2) lack of appropriate controls. [95]

6 – “Furthermore additional studies are required to assess the influence of NF1 pathogenic variants identified in patients undergoing clinical genetic testing on breast cancer risk in individuals without clinical evidence of NF1.’ -The authors may have also missed this recent publication on genotype-phenotype -https://www.ncbi.nlm.nih.gov/pubmed/30530636”

Response: Thank you again for pointing out this important and interesting study. This study has actually not been published yet, but is available by Epub ahead of print. It has also been included in the discussion section of the manuscript.

Pg. 18: Additionally, a study conducted by Frayling et al. evaluating NF1 constitutional mutation types and breast cancer risk in patients with NF1 and breast cancer showed that different NF1 variants demonstrate different risk of breast cancer and that nonsense and missense mutations may be associates
with a higher breast cancer risk. [96]