Author’s response to reviews

Title: Are Rare Cancer Survivors at Elevated Risk of Subsequent New Cancers?

Authors:

Dianne Finkelstein (dfinkelstein@mgh.harvard.edu)
Nora Horick (nhorick@mgh.harvard.edu)
Ritesh Ramchandani (rramchan@sdam.harvard.edu)
Kristina Boyd (kristina.lynn.boyd@gmail.com)
Huma Rana (humaq_rana@dfci.harvard.edu)
Brittany Bychkovsky (bbychkovsky@partners.org)

Version: 1 Date: 16 Jan 2019

Author’s response to reviews:

Response to Reviews of Manuscript Number: BCAN-D-18-02937: by D Finkelstein et al:

Are Rare Cancer Survivors at Elevated Risk of Subsequent New Cancers?

Gregory Eastham Gilbert, EdD, MSPH (Reviewer 1)

“Your efforts to produce error-free work is appreciated.” Thank you!

Abstract: Requested changes in all sections of the abstract have been made (and are highlighted in yellow in the document). Also a typo in the confidence interval is corrected in line 48.

Background: Wording changes requested in lines 60 and 69 have been made. Requested reference is now given in line 85. Clarification of the comparison population is now in lines 90-92 (indicating that we are doing the comparison you suggest in your review).

Methods: Modification of “awkward line” now appears in lines 114-115.

Results: Table 1 percentages and frequencies are given and title is changed. Also use of N (uppercase) is consistent now. The requested N associated with the percent are now is given in lines 142-3.

Discussion General Comments:
1. Mathematical operators such as ">"are replaced by words now in lines 202-205.

2. Please compare and contrast with existing literature. Where does your work fit in with what has been written? Response: As we note on lines 200-202, there is literature on risk of subsequent cancer in more common cancers (and even in some less common cancers), but we found no literature on the risk of subsequent cancer for a population with rare cancer. This is the analysis that is needed because each cancer type is too rare to provide a sufficient population to study this risk over time.

3. Synthesize results with a "clinical significance" interpretation of the findings. Response: The Conclusions were modified to include this in new lines 244-249.

4. Elaborate on how limitations may have affected your results.

Response: This is now done in new lines 207-210 and 219-220.

To the Reviewer: These were excellent suggestions. Thank you for a thorough review.

Laura Mercatali (Reviewer 2):

“These interesting results could represent a relevant information in the field of rare diseases, in which we had not previous studies about a possible multiple tumors.” Thank you; we agree.

1. Report the specific rare tumors: This information is in Tables A1-A3 (Supplement)

2. More than one rare cancer could be associated with familiarity syndrome like MEN or VHL. The only anamnestic data are not sufficient to consider it. Response: We do not have these data and note this in lines 217-19.

3. Authors should suggest testing mutational panels: This is now in our Conclusions line 247-8.

4. Furthermore rare tumors classification have further improved in 20 years. This should be considered and samples should be revised according to new classification. Response: This is in lines 248-9.

To the Reviewer: Thank you for your comments. They have improved our Conclusions section.

Guy Brock (Reviewer 3):

“Overall I found the methodology and corresponding results and conclusions appropriate, though the presentation needed improvement and clarification in places.” Thank you.
Major Comments

1. It's unclear to me how they are explaining the impact of multiplicity of cancers because they do not explain the comparator groups, and it seems they are reporting results from two different models. A formal description of the model(s) here with corresponding equations including the interaction terms would be beneficial.

Response: All of the (six) prior cancer history and multiplicity variables are in a single model which is now described in lines 175-9 in the Results.

2. Table A3 is interesting and should be elaborated on further. The authors state that there is little difference between the rare and common cancer types, but in there is some heterogeneity. Also, it is surprising that having a prior common cancer is not at elevated risk for subsequent cancer (compared to no prior cancer). Also, confidence intervals around these HRs would be helpful.

Response: Our intention was to point out that within the rare types, the comparison of risk for subsequent (relative to prior common cancer or none) was similar, noting that the hazard ratio was generally 1-1.5, with the exception of liver (at 2.24). The fact that some risks were below 1 was a reflection of small sample size and these were not significant. In terms of the risk of prior common cancer versus unaffecteds: this could be due to our select population (with family history) and is different than reported in the literature; we discuss this in the paper lines 209-10. We do not give the confidence intervals because the p-values should be sufficient, but if the editor/reviewers wish, we can include these in table A3.

Minor Comments

3. Abstract: Risk of 47% for multiple prior rare cancers, but the 95% CI does not contain this value. Response: Typo has been fixed. Thank you!

4. Table 2: Can the authors report the total follow-up (person-years) in addition to the N. Response: Added.

5. Poisson regression was used to analyze the annual cause-specific risk for subsequent cancer; is there was any overdispersion that should be noted or accounted for?

Response: We did not use Poisson regression.

6. A robust sandwich estimator was used to account for correlation but don't mention at what level, presumably this was for subjects seen at the same academic center?

Response: We used the sandwich estimator to account for correlation due to having the same initial cancer. We have clarified this in line 125-6.
To Reviewer: Thank you for the comments on our models and results. These have improved the clarity of the paper.