Reviewer's report

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

Version: 0 Date: 22 Dec 2018

Reviewer: Guy Brock

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The authors use data from the NIH-sponsored Cancer Genetics Network (CGN) to evaluate whether subjects with a prior rare cancer were at greater risk compared to subjects with a prior common cancer. They found that subjects with a prior cancer did have an elevated risk (23%) compared to those with no prior cancer while subjects with a prior common cancer were not at elevated risk. There was a further increase in this risk with the number of prior rare cancers. Overall I found the methodology and corresponding results and conclusions appropriate, though the presentation needed improvement and clarification in places. My comments are below.

Major Comments

1. The section presenting the additional risk associated with multiple prior cancers is a bit confusing and could use clarification. The authors present that individuals with 2 or more prior cancers are at 53% increased risk (HR = 1.53) compared to 0-1 prior cancers, while 2 or more rare cancers are at 47% increased risk (HR = 1.47) compared to 0-1 prior rare cancers. The authors mention that this is additional risk but the it's unclear to me how they are making that claim because the comparator groups in the two cases are different, and it seems they are reporting results from two different models. In subsequent sentences it is explained that in fact subjects with prior common cancer(s) are at no increased risk, so it seems the 53% overall increase in risk with 2+ prior cancers is solely due to the rare cancers. I think a formal description of the model(s) here with corresponding equations including the interaction terms, etc. would be greatly beneficial to understanding the meaning of the results the authors are presenting.

2. Table 3 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 fact there are a number of rare cancers with HR for subsequent cancer (compared to common or no prior cancer) <1, so clearly
there is some heterogeneity. Also, it is interesting that while none of the common cancers (except colorectal) have significant increased risk for subsequent cancer compared to no prior cancer, all of the HRs are >1. When taken together, it is a bit 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.

Minor Comments

3. Abstract: The authors report a further elevated risk of 47% for multiple prior rare cancers, but the 95% CI does not contain this value.

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

5. The authors used Poisson regression to analyze the annual cause-specific risk for subsequent cancer, which is fine but I'm wondering if there was any overdispersion that should be noted or potentially accounted for?

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

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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