Reviewer's report

Title: TP53 mutations in ovarian carcinomas from sporadic cases and carriers of two distinct BRCA1 founder mutations; relation to age at diagnosis and survival

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Reviewer: David Goldgar

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General
This paper examines the correlation of the presence/absence of somatic TP53 mutations with survival in ovarian cancer patients with either of the two Norwegian BRCA1 founder mutations as well as a larger set of non-hereditary ovarian cancer cases. The authors find that the presence of a TP53 mutation is associated with poorer survival in BRCA1 carriers but not in the "sporadic" group. There are several major problems with the paper as defined below.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. Perhaps the most severe problem with the paper is the uncertainty about which tumours in fact have a TP53 mutation. The fact that eight samples had aberrant TGGE bands but for which sequencing failed were counted as TP53 mutation positive is problematic, given that 5 of the 18 (27%) sequences that did work were either silent or intronic variants probably not associated with cancer. In my view these either have to be treated as missing data or the study should compare tumors with aberrant TGGE shifts versus those that don't. An alternative (but more complicated approach is to use some sort of Monte-Carlo sampling procedure which properly accounts for the possibility that the shift is not a true TP53 mutation. In any case to include them as mutation positive seems incorrect.

2. The analysis of age at diagnosis needs to be clarified. In the title one gets the impression that the focus of the paper will be on the relationship of TP53 mutations to age at diagnosis, yet the figure seems to be relating age at diagnosis to survival in two groups BRCA1 carriers and sporadic patients. Moreover, it is not at all clear what is being graphed or how the data were analyzed; it is not indicated on the graph which of the survival points are censored. I found it difficult to understand the point of the age at diagnosis analyses since it seemed to have very little to do with TP53 status. There seemed to me to be no significant differences in survival so I am not sure this is even worth including as a major focus of the paper.

3. The authors claim that the sporadic and hereditary tumours were matched for grade and histology. However, there was a far higher proportion (32% vs. 13%) of grade 1-2 tumours among the sporadic cases compared to familial cases (p=0.05). Moreover, they are also not well-matched for stage (p=0.05), which is problematic for the comparison of age of onset vs survival between these two groups of patients. Perhaps the authors could do a better job of matching even if this would reduce the numbers of sporadic tumours in the study.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. In table 1, I believe the authors have the age at diagnosis columns reversed for familial and sporadic tumours.
2. page 7. More details on the ascertainment of cases included in the study should be provided. Are the 38 familial cases all such cases identified in the pedigrees with these two founder mutations, or were living cases more likely to be included? Are the 106 sporadic all cases identified in the Radium hospital during a defined period?

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests.