Reviewer's report

Title: Founder mutations in BRCA1/2 are not found at higher frequency in Canadian Ashkenazi Jewish men with prostate cancer

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Reviewer: Hanna Rennert

Level of interest: not specified

Advice on publication: Other (see below)

The authors in this study screened 150 Ashkenazi Jewish Canadian patients for the existence of the three frequent founder mutations in BRCA1/2. They did not find a significantly higher number of prostate cancer patients carrying these mutations compared to the reported frequency of the same mutations among controls. The authors also performed a meta-analysis of association of BRCA1/2 mutations and prostate cancer, which allowed increasing the sample-size and power of the statistical analysis. The studies, however, listed in the controls section of Table 1 do not include the appropriate controls from the corresponding studies listed under cases, with the exception of one study by Hubert et al.

This recent study conducted by Hamel et al. also does not include any matched controls. Instead, BRCA1/2 mutations frequency among controls is mostly based on the study reported by Struwing et al (1997). The authors, however, do not provide any information in this paper regarding the nature of these controls. Are they matched controls from a case-control study (then, where are the cases?), or do they represent a large population of males and females screened for BRCA1/2?

Compulsory revisions:

1. Therefore, if the studies listed in Table 1 have matching controls please include BRCA1/2 frequencies also for these studies.

2. If most of these reported studies do not have matching controls, please include more information regarding the control population of Struwing et al., which you are using for calculating the frequencies of BRCA1/2 mutations in the control population in this paper.

3. The title of the paper "Founder mutations in BRCA1/2 are not found at higher frequency in Canadian Ashkenazi Jewish men with prostate cancer" is not accurate and, therefore, needs to be changed because BRAC1/2 frequencies were not studied in Canadian Ashkenazi Jewish men without prostate cancer.

4. Did this study had institutional review board (IRB) approval? It is also not indicated whether the patients were appropriately counseled. Please include this information.

5. PAR%- Please check again the formula provided in the Results and Discussion section. It seems
that some numbers got deleted.

6. Some other studies do seem to find some association of BRCA1/2 mutations with prostate cancer. Gayther et al. (Cancer Res., 15; 60(24):7185, 2002), for example, notes that germ-line mutations in BRCA2 may account for about 5% of prostate cancer in familial clusters. The PAR% values for prostate cancer attributed to BRCA1/2 mutations in your paper, however, are less than 1%. Do you have any thoughts as for the reasons for these discrepancies?

Discretionary revisions:

Some of the listed studies suggest that there may be some association of BRCA1/2 mutations with age of onset and disease severity. Have you noted such an association in your patients?

Competing interests:

None declared.