Reviewer’s report

Title: Somatic Variants of Potential Clinical Significance in the Tumors of BRCA Phenocopies

Version: 0 Date: 09 May 2019

Reviewer: Pål Møller

Reviewer's report:

The first sentence: 'Cancer predisposition in hereditary breast and ovarian cancer (HBOC) syndrome is usually caused by pathogenic germline mutations in the BRCA1/2 genes (gBRCA mutations) and is inherited in an autosomal dominant pattern.' is problematic because it introduces the concept HBOC as undefined but 'usually caused by'. As a starting point for a scientific paper this is not acceptable: logical concepts are to be defined. The other problem is that inherited variants are not mutations, an inherited variant demonstrated to cause disease is by convention denoted a pathogenic variant. The novelty 'gBRCA mutations' is not acceptable. Further in the first section of the intro the risk for carriers of pathogenic variants of both BRCA1 and BRCA2 are pooled together, but they are different and they cause two different biological forms of breast cancers which need different treatments and have different prognoses.

In the next section phenocopy is defined as 'affected by an HBOC-associated cancer', which illustrates the problems above: pathogenic variants of BRCA2 may cause prostate and pancreatic cancer, but not so for pathogenic variants of BRCA1. Is a prostate cancer in a family with a pathogenic variant of BRCA1 a phenocopy??

The rest of the intro is to this referee speculative. This might have been OK but is not when the major problem is overlooked: In the early days and still today, most families/cases were selected for genetic testing because of aggregation of cancers: Seemingly very high penetrance for HBOC and/or many cancer cases in general, and some had cancers in both the maternal and paternal lineages. All these selection models indicate that many of the families might have more than one cancer predisposing inherited genetic variant which may both cause cancer in the absence of the major gene (BRCA1/2) and modify the penetrance of the major gene (cfr CIMBA reports). Not only is these arguments lacking, there are a large number of references which should have been indicated, but which are lacking.

Methods:' tested negative for a known familial mutation' is not good enough: was the carrier with the pathogenic variant (not 'familial mutation' and which should have been the gBRCA mutation in the wrongful nomenclature defined above) the mother, or a distant relative, and to which degree did the family histories allow for more than one disease-causative genetic variant segregating in the family?
Results: Diagnoses in the selected patients studied are not results, they were selection criteria, endometrial cancer is not a phenocopy of HBOC.

Discussion: 'The familial mutations in 6/11 cases' is unclear - do they mean the ROS1 variant found in 6/11 cases studied? If so it is a variant frequently seen in the tumours, but there is no information that this was inherited? If it was, what is the prevalence of this variant in the population studied: Is it a de-novo mutation in the tumours, or an inherited variant. Without contrast information it is difficult to consider the impact of this finding.

'It is quite possible that a complex cancer phenotype is not driven solely by a single genetic or epigenetic variant, even in the presence of a highly penetrant familial mutation' is an understatement: HBOC in carriers of pathogenic BRCA1 variants are caused by the combination of 46XX and the BRCA1 variant. The CIMBA reports have presented many interacting genetic variants. The discussion is, as indicated above, out of frame with current knowledge.

Conclusions: 'An initial hypothesis that BRCA phenocopies were secondary to chimerism was not confirmed in our previous study.' is OK. For the rest, there are some findings of possibly de-novo mutations in tumours which are difficult to interpret because there is neither the relevant family histories, testing of relatives, testing of blood/normal tissue, nor information of population prevalences of the variants if they were to be inherited.

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