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BRCA1/2 mutations and *de novo* hematologic malignancies: true, true and not clearly related

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Stubbins and colleagues sought to evaluate whether individuals with germline \textit{BRCA1} or \textit{BRCA2} (gBRCA1/2) pathogenic variants (PVs) have an independent risk of developing \textit{de novo} hematologic malignancies (HM) in addition to therapy-related neoplasms\cite{1}. In this single-institution retrospective study, the authors identified 25 patients with gBRCA1 (14) or gBRCA2 (11) PVs concurrent with a HM diagnosis. Eight of 14 (\textit{BRCA1}) and eight of 11 (\textit{BRCA2}) patients had \textit{de novo} HM, rather than therapy-related HM. These patients constituted 1.1\% of patients with HMs seen over eight years. Leukemic cells from three of 14 (21\%) patients with \textit{BRCA1/2} PVs had loss of heterozygosity (LoH) of the wildtype allele. In addition to therapy-related hematologic malignancies in \textit{BRCA1/2} carriers\cite{2}, patients with \textit{BRCA1/2} PVs developed \textit{de novo} HMs of various types. Most literature examining \textit{BRCA1/2} and HM focuses on therapy-related neoplasms, so the characterization of \textit{de novo} HM is of interest. This study ascertained patients based on the presence of a HM providing a valuable perspective on gBRCA1/2 associated cancers.

The development of HM in patients with PVs in gBRCA1/2 could either be: 1) incidental, due to a risk similar to the general population\cite{3} or 2) causal, based on the gBRCA1/2 PV. Differentiating between these two possibilities is the greatest clinical concern to patients and providers, which the present report is neither designed nor powered to address.

The authors suggest that the relative frequency of gBRCA1/2 PVs is enriched in their HM population comparing to a reference (gnomAD) population. However, without ancestry matching, it is impossible to accurately determine if it truly is higher as the frequency of gBRCA1/2 PVs varies among populations; 1:175 individuals\cite{4} in non-Finnish Europeans (0.6\%) and 1:40 in Ashkenazi Jews (2.5\%)\cite{5}. The report of 1.1\% rate of gBRCA1/2 PVs in HMs could be based on representation of individuals from both populations, and enriched due to referral bias.

In a significant proportion of tumors occurring in patients with \textit{BRCA1/2} PVs, the mutant BRCA protein is biologically neutral, with tumor pathogenesis occurring independently of, rather than driven by, gBRCA1/2. In an analysis evaluating germline blood and matched tumor tissue from over 17,000 cancer patients among whom 472 harbored a gBRCA1/2 PV, selective pressure for biallelic inactivation, zygosity-dependent phenotype penetrance, and poly-ADP ribose polymerase inhibitor (PARPi) sensitivity was only observed in tumor types classically associated with \textit{BRCA1/2}, i.e. breast, ovary, prostate or pancreas cancers\cite{3}.

Arguing \textit{against} BRCA as a major driver of the observed \textit{de novo} HM is the presence of LoH in only three of 14 evaluated samples in the study cohort. It is known that classically \textit{BRCA1/2}-associated solid tumors often (though not always) demonstrate LoH, whereas solid tumors occurring with, but not driven by, BRCA do not\cite{6}. The level of LoH observed in this study is consistent with chance, similar to the level observed with benign gBRCA1/2 variants in a larger dataset\cite{3}. As noted by the authors, both determining whether this level is higher than observed in HM with benign gBRCA1/2 variants and evaluating the role of epigenetic silencing should be done. In classically associated \textit{BRCA1/2}-associated tumors with and without LoH, additional factors often support BRCA as a driver of tumor pathogenesis such as vertical transmission, early age of onset, and phenotypic tumor characteristics including homologous recombination deficiency or PARPi sensitivity. This article does not report whether the study cohort or the observed \textit{de novo} HM display these features.

The many HM types reported is inconsistent with BRCA as a major driver of pathogenesis. For solid tumors, \textit{BRCA1/2} PV are associated with very specific tumor types – for example, high-grade serous ovarian cancer and pancreatic ductal adenocarcinoma are \textit{BRCA1/2}-associated neoplasms, whereas low-grade, borderline, and germ-cell ovarian and pancreatic neuroendocrine cancers are not.
Furthermore, PVs in \textit{BRCA1} and \textit{BRCA2} have non-identical cancer risk profiles. The lumping of 10 different HM diagnoses and consideration of \textit{gBRCA1/2} together are convenient, however, their consideration in aggregate detracts from a specific causal relationship.

Previously published studies have rigorously examined qualitative and quantitative cancer risks conferred by \textit{gBRCA1/2} PVs. A study including 3184 \textit{BRCA1} and 2157 \textit{BRCA2} families from the Consortium of Investigators of Modifiers of \textit{BRCA1/2} (CIMBA) estimated absolute risks for 22 first primary cancer types, adjusting for family ascertainment\cite{7}. No increased risk of leukemia (\textit{BRCA1}: RR 0.90, 0.36 to 2.26, \textit{p}=0.82; \textit{BRCA2}: 0.91, 0.29 to 2.85, \textit{p}=0.87), lymphoma (\textit{BRCA1}: RR 1.03, 0.33 to 3.22, \textit{p}=0.96; \textit{BRCA2}: 0.97, 0.16 to 5.87, \textit{p}=0.97), or multiple myeloma (\textit{BRCA1}: RR 3.06, 0.83 to 11.26, \textit{p}=0.09; \textit{BRCA2}: RR 0.84, 0.10 to 7.31, \textit{p}=0.87) was reported. Stubbins and colleagues note that this study ascertained patients based on known personal or family history of breast or ovarian cancer, with the possibility of pre-selection for a specific disease phenotype. Although bias is possible, it is extraordinarily unlikely that clinically meaningful risks of HM would have been undetected. Furthermore, characterization of cancers in a cohort of nearly 7,000 men with \textit{gBRCA1/2} PV showed 51 cases of HM (all subtypes) among 1634 cancers noted (3.1\%)\cite{8}. By comparison, lymphoma, leukemia and multiple myeloma are estimated to comprise 9.4\% of new cancers in United States in 2023\cite{9}. Therefore, even in a \textit{BRCA1/2} population without a risk of female breast or ovarian cancer, HM are not overrepresented.

We therefore read this exploratory study with interest, but also with concern that its findings, based on 16 patients with \textit{de novo} HM from a single institution, may be misinterpreted or extrapolated to indicate a causal relationship between \textit{gBRCA1/2} and HM in general. The preponderance of currently published data from rigorously conducted studies refutes such causality. The current report, while thought-provoking, does not provide the breadth or depth of evidence necessary to contradict existing data. We agree with the authors’ conclusion that examining study populations specifically ascertained to look at inherited predispositions to HM, and families with \textit{BRCA1/2} PVs and multiple cases of HM, would be of interest. However, we wish to reassure the readership and the \textit{BRCA1/2} community that although this paper by Stubbins and colleagues demonstrates that individuals with \textit{BRCA1/2} PVs are not exempt from HM risk, it does not substantiate a \textit{BRCA1/2}-associated general HM predisposition.
References: