Individual and familial phenotype in hereditary ovarian cancer


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Background: Germline mutations impacting homologous recombination repair (HCR) have been associated with predisposition to breast (BC) and ovarian cancer (OC), and more than 1/5 of OC have hereditary susceptibility (HOC). Other genes than BRCA have been associated with HOC.

Methods: All index, consecutive, non-mucinous OC patients (pts) counselled between September 2016-December 2017 were tested upfront for a panel testing (PT) including BRCA1, BRCA2, RAD50, RAD51C, RAD51D and BRIP1 (BRCA Hereditary Cancer MASTER Plus methodology). We analyze the molecular results, their clinical characteristics and family history (FH).

Results: One hundred and one female pts with OC diagnosis consented to PT. Pathogenic variants (PV) were found in 19 pts (18.8%); BRCA2 – 8 (42%), BRCA1 – 5 (26%), RAD51C – 3 (16%), RAD51D – 2 (11%), RAD50 – 1 (5%). The majority of these OC had been previously classified as high-grade serous (HGS) (n = 13 - 68%). We identified 2 pts with low-grade serous carcinoma (LGSC) with pathogenic variants (1 BRCA2; 1 RAD51C). Although median age of diagnosis (MAD) was lower for BRCA2 (55 years) and BRCA1 (58 years) than “non-hereditary” and RAD50/RAD51C/RAD51D pts (both groups with MAD of 63 years), difference was non significant (p = 0.21). As for FH (defined as: other OC and/or BC < 50 years and/or male BC), only 54% of BRCA1/2 pts and none of RAD50/RAD51C/RAD51D had a positive FH. Eighteen percent of “non-hereditary” OC pts had positive FH. With a median follow up of 5 yrs, 63% of pts harboring PV and 50% of those with no PV relapsed, with 2 pts having central nervous system relapses (1 - RAD51D and 1 - RAD50). All but 7 pts were alive at analysis time, only one with a germline mutation impacting HCR (RAD50 mutation).

Conclusions: Family history was not associated with detection of germline pathogenic variants and should not be a criteria for selection of OC for genetic testing. While the inclusion of other genes in our panel may increase our detection rate, excluding LGSC (not included in some guidelines as candidates for testing) would not detect an undetermined number of pts, since the association between LGSC and HOC is not clarified. Longer follow up may help clarify if there is a genotype/phenotype correlation regarding patterns of relapse in hereditary ovarian cancer.

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