Breast and Ovarian Cancer Risks Beyond *BRCA1/2* from a Cohort of 15,000 Women Undergoing Multigene Panel Testing

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Multigene panel testing (MGPT) for hereditary cancer is increasing in popularity in the USA. Many panels include genes identified as hereditary breast and/or ovarian cancer (HBOC) genes despite limited data regarding the precise cancer risks associated with mutations in these genes. This study examined clinical histories, ethnicity, and test results from a cohort of 15,083 individuals who underwent MGPT of up to 20 genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, TP53) using the BreastNext and OvaNext panels. The majority of individuals were from high-risk breast and/or ovarian (Br/Ov) cancer families, with 92.4% of all probands meeting National Comprehensive Cancer Network HBOC testing criteria. Pathogenic mutations were identified in 9.4% of the overall cohort. No ethnicity specific enrichment of mutations was observed. To further quantify gene-specific Br/Ov risks, a series of case-control analyses were performed comparing the frequencies of inactivating mutations and previously classified pathogenic or likely pathogenic missense alterations between cases from Br/Ov MGPT and controls from the Exome Aggregation Consortium (ExAC) database. Estimated risk ratios (RR) for Br/Ov cancer in well-studied genes were consistent with previous reports, including an increased breast cancer risk but no increased ovarian cancer risk associated with CDH1, ATM, and CHEK2 mutations. Ovarian cancer risk was significantly ($p<0.001$) increased for mutations in RAD51D (RR >9), RAD51C (RR >8) and BRIP1 (RR >7). Additional results of interest included a significantly increased risk of breast cancer at age >50 for NF1 carriers, breast cancer for MSH6, breast cancer <50 for RAD51D, and ovarian cancer for PALB2. This large breast and ovarian cancer case-control analysis provides useful data for many HBOC genes previously lacking risk estimates, and should prove useful for clinical risk management of patients after MGPT.