Breast and ovarian cancer risks associated with cancer predisposition gene mutations identified by 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. Here we report on results from BreastNext and OvaNext panel testing of 20 genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, TP53) in a cohort of 15,083 individuals. 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.

To estimate gene-specific breast and ovarian cancer risks, case-control analyses were performed comparing the frequencies of pathogenic mutations from Caucasian breast or ovarian cancer cases from BreastNext and OvaNext with frequencies from Caucasian, non-Finnish, non-TCGA controls from the Exome Aggregation Consortium (ExAC) database. Mutations in the well studied ATM and CHEK2 genes were associated with moderate risks (OR>2) of breast cancer and mutations in PALB2 were associated with high-risks (OR>5) of breast cancer, consistent with previous reports. In addition, the study suggested that pathogenic mutations in MSH6, RAD51D, CDH1, and NF1 are associated with moderate to high risks of breast cancer. In contrast, RAD51C, RAD51D, and BRIP1 mutations were associated with high risks of ovarian cancer, PALB2 mutations were associated with moderate risks, but ATM and CHEK2 mutations were not associated with increased ovarian cancer risk. In addition, modeling of missense mutations in the predisposition genes using in silico prediction algorithms suggested that missense mutations in CDH1, CHEK2, MSH2, and MSH6 are associated with moderate risks of breast cancer and missense mutations in RAD51C increase risks of ovarian cancer. This large breast and ovarian cancer case-control analysis provides useful data for many predisposition genes previously lacking risk estimates, and should prove useful for clinical risk management of patients after clinical panel testing.