Abstract Preview

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Cancer risks associated with predisposition gene mutations identified by hereditary cancer panel testing of 85,000 patients

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Clinical genetic testing of individuals with a personal or family history of breast and ovarian cancer using panels for *BRCA1/2* and other candidate cancer predisposition genes have become routine clinical practice. While the cumulative lifetime and age specific risks associated with mutations in *BRCA1/2* in high-risk families and in the general population are well understood, the risks of breast cancer associated with mutations in many of the other panel genes are not well defined.

To estimate risks of breast, ovarian, and other cancers associated with inherited deleterious mutations in cancer predisposition genes we utilized results from 85,379 hereditary cancer panel tests performed by Ambry Genetics. Among these 63,368 reported a personal history of cancer other than basal skin cancer, including 46,320 breast cancers, 6194 ovarian cancers, 4896 colorectal cancers, 2883 endometrial cancers, 1252 pancreatic cancers, 312 gastric cancers, along with smaller numbers of other cancers. Of those with breast and/or ovarian cancer, greater than 90% met National Comprehensive Cancer Network HBOC testing criteria.

To estimate gene-specific risks for individual cancers, case-control analyses were performed comparing the frequencies of pathogenic mutations from Caucasian cancer cases with frequencies from Caucasian, non-Finnish, non-TCGA controls from the Exome Aggregation Consortium (ExAC) database. Using breast and ovarian cancer as examples, mutations in ATM and CHEK2 genes were associated with moderate risks (Relative Risk (RR)>2) of breast cancer and limited risk of ovarian cancer, as expected. Pathogenic mutations in CDH1, NF1, and RAD51D were also associated with moderate risks of breast cancer, whereas PALB2 was associated with high risks (RR>5.0) of breast cancer. In contrast, RAD51C, RAD51D, BRIP1, and PALB2 mutations were associated with high risks of ovarian cancer. Risks for several cancers associated with mutations in the various panel-testing genes will be presented. This large clinical testing dataset in combination with public controls provides useful data for many predisposition genes previously lacking risk estimates, and should prove useful for clinical risk management of patients with inherited mutations in these genes.

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