Association between mutations in genes from NGS multi-gene panels and breast and ovarian cancer risk

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Background: As *BRCA1/2* mutations are responsible for only part of familial breast cancer (BC) and ovarian cancer (OC) cases, researchers and clinicians are looking for other BC/OC risk genes. Recent progress and decreasing cost of the next generation sequencing (NGS) has allowed to expand the range of examined genes. However, the inclusion of additional genes to the NGS multi-gene panels (MGPs), is not always supported by strong genetic or statistical evidences and most of the genes still have to be considered as "candidates".
Aim of the study: We aimed to estimate a reliable BC and OC risk associated with mutations in genes repeatedly employed in MGPs.
Methods: We accomplished a wide-scale meta-analysis of results from 48 MGP-based studies, that analyzed BC and OC patients. The mutation frequency of ~120,000 BC/OC cases and ~120,000 controls, extracted from public gnomAD database, were used to estimate BC and OC association with mutations in 37 genes.
Results: In total, 13 and 11 of the analyzed genes were significantly associated with an increased BC and OC risk, respectively. We noticed that mutations in a few genes are attributed to a high BC risk, at a level similar to that of *BRCA2* mutations. Furthermore, our results revealed that *CDKN2A*, not often mentioned in the context of BC, can be classified as a high-risk gene. The other striking observation of our study is the substantial difference in the profile of genes contributing to either BC or OC risk. We showed that mutations in several genes much more strongly predispose to OC than BC. Extreme examples are mutations in *RAD51D*, *RAD51C*, and *NBN* that are specific to OC and do not predispose to BC at all. Additionally, what is equally important, the analysis indicated which genes, frequently used in MGPs, are not associated with BC/OC risk.
Conclusions: In summary, our results define with high confidence the role of several genes in the genetic predisposition to BC and OC. The practical implication of our results is the support that they provide for a substantively justified interpretation of diagnostic results.

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