Editorial Note on Genetic Risk Assessments of Cancer

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Editorial

Pathogenic germline mutations in cancer-predisposition genes found in hereditary cancer multigene testing panels have been linked to an increased risk of breast cancer. Identification of pathogenic variants in predisposition genes has benefited carriers of pathogenic variants in BRCA1 and BRCA2 by improving access to risk-reducing prophylactic surgery and targeted therapies, as well as access to enhanced mammography and Magnetic Resonance Imaging (MRI)-based screening among carriers of pathogenic variants in several established breast cancer–predisposition genes.

The overall prevalence of harmful mutations in these genes has been estimated to be 7 to 10% in breast cancer patients. However, these breast cancer prevalence and risks are based on high-risk populations enriched with women who had a family history of breast and ovarian cancers, were diagnosed with breast cancer at a young age, had oestrogen receptor (ER)-negative tumours, or had founder mutations. Only small-scale studies have looked at pathogenic variations in multigene panels in women with breast cancer who were not chosen based on family history or age at diagnosis. As a result, existing risk estimates for breast cancer based on predisposition genes have dubious applicability to the general population.

Hereditary predisposition is observed in about 10% of all breast cancer cases. The majority are linked to germline mutations in high-penetrance genes like BRCA1 and BRCA2. Since the discovery of BRCA1 and BRCA2, genetic testing has become a standard aspect of clinical care for people who may be predisposed to hereditary breast cancer. More than 30 possible breast cancer susceptibility genes (BCSGs) have been proposed, including genes with high (e.g., BRCA1/2, TP53, CDH1, PTEN, and STK11), moderate (e.g., PALB2, CHEK2, ATM, and RECQL), and low-to-disputed penetrance (e.g., MLH1, MSH2, MSH6, PMS2, MEN1, and PPM1D). Among them, the top two authoritative resources, the Clinical Genome Resource (ClinGen) and the National Comprehensive Cancer Network (NCCN), have definitively established 12 genes with high or moderate penetrance for breast cancer.

Pathogenic mutations in a BCSG can increase the risk of other diseases as well. CDH1, for example, is linked not just to an elevated risk of breast cancer, but also to a susceptibility to stomach cancer. Furthermore, certain BCSGs, such as TP53, are responsible for rare hereditary cancer syndromes, such as Li-Fraumeni syndrome. Individuals with this syndrome are at an extremely high risk of acquiring a variety of cancers, including but not limited to breast cancer, sarcoma, brain cancer, leukaemia, lung cancer, and adrenocortical cancer. As full panel genetic testing becomes more common, doctors are increasingly challenged with advising mutation carriers on genes they may be unfamiliar with or influencing cancer susceptibility in organs outside their speciality.

In addition to NCCN and ClinGen, a number of existing resources, including but not limited to Genetics Home Reference, Online Mendelian Inheritance in Man (OMIM) GeneCards, and Gene-NCBI, detail the disorders related with each gene. The gene-disease connections documented in these six resources, on the other hand, are frequently imprecise, partial, or perplexing. BRCA2 is associated with melanoma in NCCN and Genetics Home Reference, but not in other genetic resources such as ClinGen, OMIM, GeneCards, or Gene-NCBI. Furthermore, some gene-disease connections, such as the relationship of CHEK2 with stomach cancer, which has been proven with high likelihood in the literature, are not detected in any genetic database. This creates a significant quandary for doctors who are tasked with identifying and assessing gene-disease relationships that require management in clinical practise..

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