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A CRAIN FAMILY BRAND

Cancer Predisposition Patterns Spelled Out in Germline Risk Variant Studies

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NEW YORK – Independent research teams have gained new insights into the prevalence and apparent cancer risk of a range of germline pathogenic variants in genes previously implicated in breast cancer and other cancer types.

In the first of these studies, appearing in *JAMA Internal Medicine* on Friday, a team led by investigators at the University of California, San Diego outlined secondary findings from the WISDOM ("women informed to screen depending on measures of risk") randomized clinical trial that included nearly 23,100 women between the ages of 40 and 74, who have received germline genetic testing for BRCA1, BRCA2, ATM, CHEK2, PALB2, CDH1, PTEN, STK11, and TP53 through Color Genomics' CLIA-certified, CAP-accredited lab.

The participants did not have a personal history of breast cancer, the team noted. Nearly 15 percent of individuals in the study had one or more parent with Jewish ancestry, researchers noted, and WISDOM participants were more prone to a family history of breast cancer than individuals from the general population, based on diagnostic rates reported in the past.

"This analysis describes the prevalence of [pathogenic variants] in a large cohort of women offered criteria-independent genetic testing and the relationship of test positivity to family history and other participant characteristics," senior and corresponding author Lisa Madlensky, a medicine researcher at UCSD, and her colleagues wrote.

Using targeted multigene panel next-generation sequencing, the team found 714 women carrying pathogenic or likely pathogenic variants in one of the nine genes assessed — a group that included 109 individuals who previously received pathogenic variant results.

The team found that pathogenic or likely pathogenic variants most frequently turned up in genes such as CHEK2 or ATM, which had pathogenic variant rates of 1.5 percent and 0.4 percent, respectively.

On the other hand, higher-penetrance genes such as BRCA1/3 or PALB2 had lower rates of germline pathogenic or likely pathogenic variants, with risky BRCA1 variants turning up in 0.1 percent of those tested, followed by rates of 0.2 percent and 0.4 percent for PALB2 and BRCA2.

"The identification of BRCA1, BRCA2, and PALB2 [pathogenic variant] carriers without a family history of breast cancer highlights an important implementation gap in testing guidelines," the authors suggested, adding that the "steadily decreasing cost of genetic testing offers new opportunities for broader application, especially given the younger mean age of diagnosis and risk of fast-growing and aggressive cancers in many of these [pathogenic variant] carriers."

Pathogenic or likely pathogenic variants were even less common in the CDH1, PTEN, STK11, and TP53 genes, with frequencies of less than 0.1 percent apiece, the researchers reported.

When it came to cancer risk associated with the genes, meanwhile, the team noted that nearly one-third of pathogenic or likely pathogenic variant carriers did not have Jewish ancestry or a family history of breast or ovarian cancers affecting first- or second-degree relatives, including male relatives with breast cancer.

Together, the authors suggested, their findings "demonstrate that relying on a reported family history of cancer has limitations in identifying women who carry a [pathogenic variant], and criteria-independent testing would broaden the group who could benefit from evidence-based cancer surveillance and risk-reduction interventions."

For another *JAMA Network Open* paper published on Monday, investigators at the National Institutes of Health brought together exome sequence data and electronic health record data for 469,765 UK Biobank participants and some 167,050 individuals enrolled in the Geisinger MyCode effort to search for individuals carrying heterozygous germline alterations affecting CHEK2, a tumor suppressor gene implicated in conditions such as breast cancer or prostate cancer.

"In this case-control study, we evaluated cancer risk and survival in individuals with heterozygous CHEK2 variants using the novel genome-first approach in [two] well-powered cohorts," senior and corresponding author Douglas Stewart, a researcher with the clinical genetics branch of NIH, and his colleagues wrote.

The team saw an overall increase in cancer risk and a decreased time to cancer development in the 3,232 UK Biobank and 3,153 MyCode participants carrying pathogenic, missense, or truncating variants affecting one copy of the CHEK2 gene, particularly when it came to the risk of breast cancer, prostate cancer, kidney cancer, bladder cancer, and chronic lymphocytic leukemia.

Even so, the authors noted that "the conferred excess cancer risk was low," coming in at an odds ratio of less than two — insights that are expected to inform the way cancer risk information is conveyed to individuals with CHEK2 risk variants uncovered through genomic testing rather than a cancer family history.

"Genomic ascertainment quantifies risk based on genotype (not phenotype)," they explained, "and thus may reduce risk inflation arising from cancer ascertainment (case and family recruitment) by personal and/or family medical history."

Finally, the team's survival comparison picked up a dip in overall survival in UK Biobank participants with pathogenic or likely pathogenic CHEK2 variants, particularly in individuals over 75, though survival patterns were similar in carriers and noncarriers in analyses of MyCode study participants.

The authors reported that there was "considerable overlap" between the degree of risk from pathogenic truncating variants (PTV) and pathogenic missense variants (PMV), with risk of PMV generally lower. "However, cancer penetrance, all-cause mortality, and all-cause mortality in individuals with cancer was not significantly different between PMV and PTV, suggesting that clinical differences between these variant types are less relevant," they noted.

The investigators cautioned that individuals of European ancestry are overrepresented in both the UK Biobank and MyCode efforts which are also expected to have ascertainment biases. Likewise, they noted that additional analyses are needed to understand the consequences of CHEK2 copy number variants.

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