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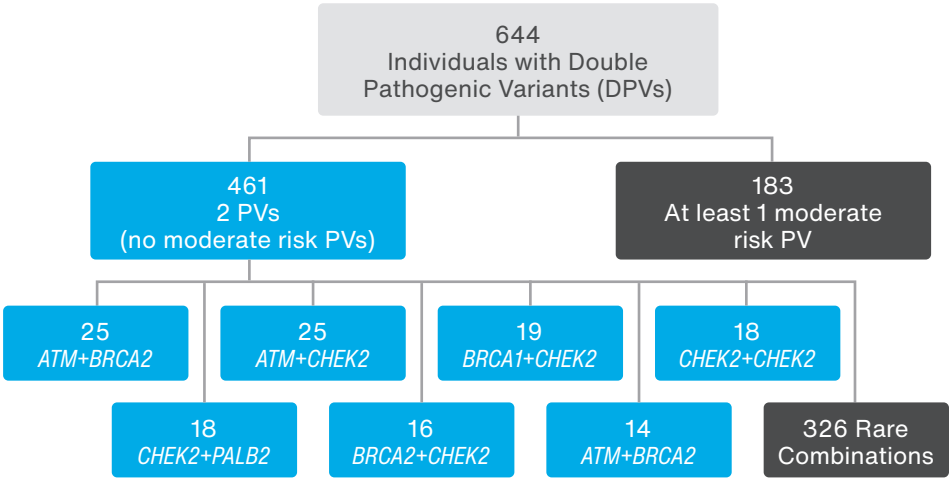
Research For Your Practice

# Double jeopardy? Exploring cancer risks in individuals with multiple pathogenic variants in cancer predisposition genes

## INTRODUCTION

What happens when hereditary cancer testing identifies not one pathogenic variant, but two? It's unclear if cancer burden is higher among individuals with double pathogenic variants (DPVs). In this study, investigators compared the age of cancer diagnosis and the number of primary tumors in individuals with DPVs compared to those with a single PV.




**IN MOST COMBINATIONS,** age at diagnosis and number of primary tumors in individuals with DPVs were similar to the high-risk single PV, and individuals with a combination including *BRCA1* were more likely to have triple negative breast cancer. Here's where we found some exceptions:

### 7 years younger

*CHEK2+CHEK2*
age at first breast cancer
40y *CHEK2+CHEK2* vs. 47y *CHEK2* single PV

### 4 years younger

*ATM+CHEK2*
age at first breast cancer
43y *ATM+CHEK2* vs 47y *ATM* or *CHEK2* single PV

**YOUNGER AGE AT DIAGNOSIS**

**MORE PRIMARY CANCERS**

### 5 times higher

*CHEK2+CHEK2*
odds ratio for multiple primaries
61% of *CHEK2+CHEK2* vs 23% *CHEK2* single PV

### *BRCA1+BRCA2*

Hormone Receptor Status mimics *BRCA2*
56% ER/PR+ in *BRCA1+BRCA2* vs 24% *BRCA1* single PV

**Reference:**

Agaoglu, N. B., Bychkovsky, B. L., Horton, C., Lo, M.-T., Polfus, L., Carraway, C., Hemyari, P., Young, C., Richardson, M. E., Scheib, R., Garber, J. E., & Rana, H. Q. (2024). Cancer burden in individuals with single versus double pathogenic variants in cancer susceptibility genes. *Genetics in Medicine Open*, 2, 101829. https://doi.org/10.1016/j.gimo.2024.101829

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