Abstract #1570

Co-occurring Pathogenic Variants in Patients with Breast Cancer

Kallie Woods MS, CGC[1], Shelly Cummings MS, CGC[1], Foluso O. Ademuyiwa, MD, MPH, MSCI[2]

1 Myriad Genetics, Salt Lake City, UT **2** Washington University School of Medicine in St. Louis, St. Louis, MO

Background

- Numerous studies have examined germline variant rates in individuals with breast cancer (BC), consistently reporting that about 5-10% carry a germline pathogenic variant (PV).[1,2]
- Although multiple PVs in a single patient have been documented, cases are rare and reported in small cohorts.
- As a result, the clinical implications of multiple PVs remain poorly understood.
- To address this gap, we analyzed a large dataset of patients with BC who underwent germline genetic testing.

Methods

- The Myriad Collaborative Research Registry v4, containing clinical, genetic, and genomic information on over 1.2 million individuals with cancer, was queried.
- The registry included data on 795,165 individuals with a BC diagnosis who completed testing at a clinical laboratory between 1996 and 2025.
- Data was assessed using descriptive statistics to understand the prevalence and characteristics of patients with multiple PVs.

Table 1. Patients with Two PVs (n=1,600)

Cohort Type	High/High Risk Gene	High/Moderate Risk Gene	High/Other Risk Gene	Moderate/ Moderate Risk Gene	Moderate/Other Risk Gene	Other/Other Risk Gene
Number of patients	198 (12.4%)	279 (17.4%)	453 (28.3%)	91 (5.7%)	386 (24.1%)	193 (12.1%)
Median Age of Cancer Diagnosis	45	48	48	48	52	54
Assigned Female at Birth	191	265	442	90	382	191
Ancestry						
White/Non-Hispanic	96	196	341	71	333	160
Ashkenazi Jewish	29	2	7	2	5	4
Hispanic/Latino	26	40	45	4	23	12
Black/African	16	16	43	5	11	11
Asian/Pacific Islander	10	4	12	2	4	0
Not specified	30	34	44	13	40	20

Table 2. High, Moderate, and Other Risk Genes

High Risk BC PVs	*BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53*
Moderate Risk BC PVs	*ATM, BARD1, CHEK2, RAD51C, RAD51D*
Other Risk PVs	*APC, BRIP1, CDKN2A P14ARF, CDKN2A P16, CTNNA1, EGFR, EPCAM, FH, FLCN, HOXB13, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, TERT, TSC2, VHL*

Results

- Among 795,165 individuals diagnosed with BC, 75,491 (9.5%) had one pathogenic variant (PV), 1,600 (0.2%) possessed two PVs, and 34 individuals carried more than two PVs.
- Of those with two PVs, the most frequent second primary diagnoses were ovarian cancer (n=84), colon adenomas/polyps (n=68), breast cancer (n=45), and endometrial cancer (n=39). (**Figure 1**)
- The median age at cancer diagnosis for patients with two PVs was 49 years. Most of these patients were assigned female at birth (n=1,561) and identified as White/Non-Hispanic (n=1,197). (**Table 1**)
- Patients with two PVs were classified into BC PV risk categories: high-risk, moderate-risk, and other-risk. For patient distribution according to these categories, refer to **Table 2**.

Figure 1. Personal History by Risk Category

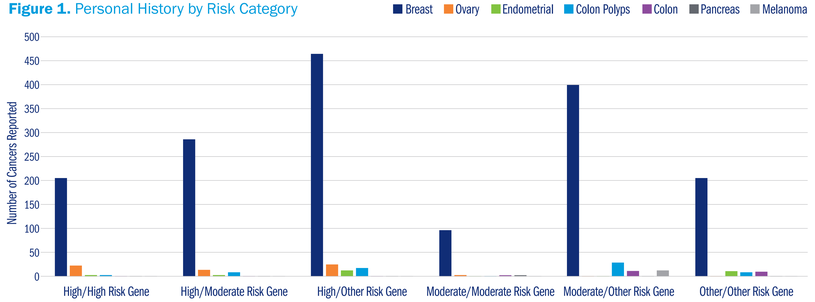
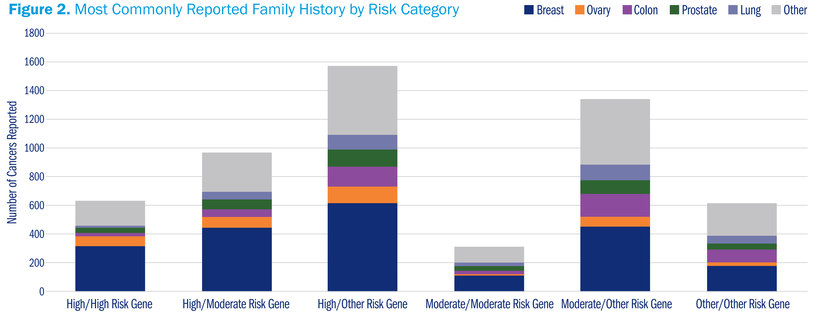
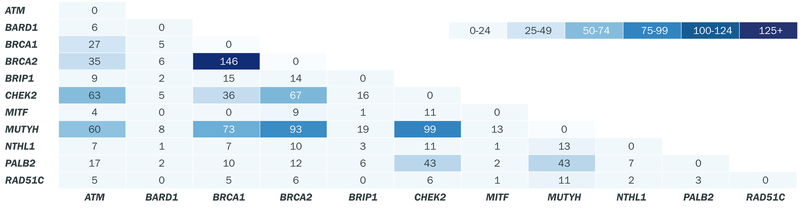


Figure 2. Most Commonly Reported Family History by Risk Category



- The largest subgroup (28.3%) comprised individuals with one high-risk and one other-risk PV. The median age at diagnosis was 48 years across most subgroups, increasing to 54 years in the other/other-risk category. (**Table 1**)
- Across all groups, a family history of BC was most frequently reported. Groups containing at least one high-risk PV commonly reported ovarian cancer as the second most prevalent family history, while colon cancer was the second most reported in groups with at least one other risk PV. (**Figure 2**)
- In the high/high-risk group, *BRCA1/BRCA2* pairings accounted for 73.7% of cases, whereas *ATM/CHEK2* comprised 69.2% within the moderate/moderate-risk group. (**Figure 3**)
  - These pairings occurred at notably higher frequencies compared to others.
  - Additionally, approximately one-third of patients with two PVs had a PV in *MUTYH*.

Figure 3. Common Gene Pairs by Risk category (n=1,600)



Conclusions

- Assessing patients with two germline PVs presents clinical and interpretive challenges.
- This study identified two co-occuring PVs at a frequency of 1,600 in 795,165 (0.2%) individuals with BC and highlights patterns suggesting that detailed personal and family history may aid in understanding these complex genetic profiles.
- Continued data collection is essential to identify subtle trends and improve risk assessment in patients with two PVs.
- Future research is needed on specific gene pairings to clarify phenotypic differences and refine risk stratification.
- The registry enabled identification of a large cohort with two PVs, laying a foundation for deeper investigation into their clinical significance.

1. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. *N Engl J Med.* 2021;384(5):440-451. doi:10.1056/NEJMoa2005936.
2. Tung N, Battelli C, et al. Frequency of mutations in individuals with breast cancer referred for *BRCA1* and *BRCA2* testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015 Jan 1;121(1):25-33. doi: 10.1002/cncr.29010. Epub 2014 Sep 3. PMID: 25186627.

Email for questions: kawoods@myriad.com