Clinical Presentation of *BRCA1* and *BRCA2* Double Heterozygous Mutation Carriers

Heidi McCoy, Kelsey Moyes, Christopher Arnell, Michelle Landon, Eric Rosenthal, Dmitry Pruss, and Richard J. Wenstrup
Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA

BACKGROUND

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is an autosomal dominant condition caused by a mutation in either the *BRCA1* or *BRCA2* gene. A mutation in either the *BRCA1* or *BRCA2* gene greatly increases an individual's risk of developing breast and/or ovarian cancer. It is estimated that 1 in 300 to 1 in 500 individuals carry either a *BRCA1* or *BRCA2* mutation, with an increased prevalence of 1 in 40 among individuals of Ashkenazi Jewish (AJ) ancestry. On occasion, individuals are observed to carry both a *BRCA1* and a *BRCA2* mutation. The literature regarding the clinical presentation of double *BRCA1* and *BRCA2* heterozygous individuals is varied and ranges from conclusions that it does not lead to more severe phenotype to it seemingly leads to higher probability of developing cancer and breast cancer at earlier ages.[1,2]

OBJECTIVE

- This study contrasts the clinical presentation of single *BRCA1* and *BRCA2* mutation carriers to double heterozygote *BRCA1* and *BRCA2* mutation (DM) carriers.

METHODS

- A retrospective review of patients' personal history of cancer was performed on patients identified with both a *BRCA1* and *BRCA2* deleterious or suspected deleterious mutation analyzed at Myriad Genetic Laboratories from January 2006 through September 2013. These patients were identified using a variety of testing strategies including single site testing, multi-site testing (analysis of three AJ founder mutations), or full sequencing and rearrangement testing. We selected 1000 patients who were identified to have a single *BRCA1* mutation and 1000 patients who were found to have a single *BRCA2* mutation who were tested during the same time period to serve as controls.

RESULTS

- We identified 196 double heterozygous mutation carriers. Of the 196 double heterozygotes, 122 (62.2%) reported a personal history of either breast cancer, ovarian cancer, or both breast and ovarian cancer. This was compared to 56.3% of *BRCA1* mutation carriers and 51.1% of *BRCA2* mutation carriers reporting a personal history of breast cancer, ovarian cancer, or both breast and ovarian cancer (see Table 1).

Table 1. Personal Cancer Histories in Single and Double Heterozygote Mutation Carriers

	BRCA1/*BRCA2* Double (N=196)	*BRCA1* Single Mutation (N=1000)	*BRCA2* Single Mutation (N=1000)
Breast Only	97 (49.5%)	415 (41.5%)	438 (43.8%)
Ovary Only	8 (4.1%)	106 (10.6%)	47 (4.7%)
Breast and Ovary	17 (8.7%)	42 (4.2%)	26 (2.6%)
Total	122 (62.2%)	563 (56.3%)	511 (51.1%)

- When comparing all breast cancers, both male and female breast cancer as well as breast cancer observed in individuals with ovarian cancer, there appears to be a slightly higher incidence of breast cancer among double heterozygous mutation carriers (Table 2).

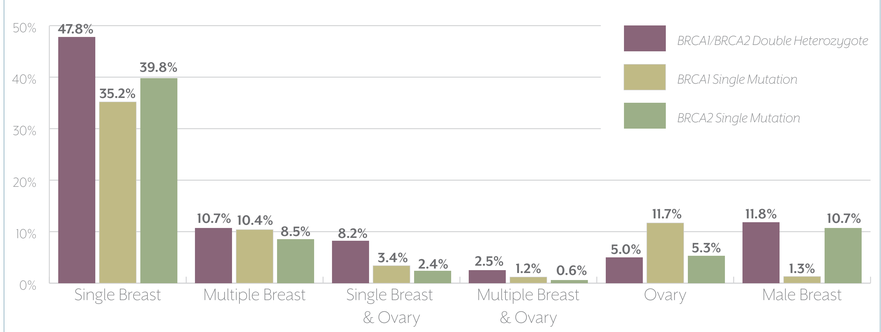
Table 2. Personal Cancer Histories in Single and Double Heterozygote Mutation Carriers

	BRCA1/*BRCA2* Double (N=196)	*BRCA1* Single Mutation (N=1000)	*BRCA2* Single Mutation (N=1000)
All Breast*	58.2% (N=114)	45.7% (N=457)	46.4% (N=464)
All Ovary*	12.8% (N=25)	14.8% (N=148)	7.3% (N=73)

*Individuals with both breast and ovarian cancer are counted in both the all breast and the all ovarian categories.

- Approximately twice as many individuals who were double heterozygous mutation carriers had a personal history of both breast and ovarian cancer (either single breast cancer or multiple breast cancers) than was seen in the single *BRCA1* or *BRCA2* mutation carriers. However, the sample size of individuals with both breast and ovarian cancer is relatively small (Figure 1).

Figure 1. Cancer Types in Single and Double Heterozygote Patients



- The reported average age of a single breast cancer diagnosis for a double heterozygous mutation carrier was 42.7 years, and 51.7 years for a single diagnosis of ovarian cancer. The reported average age of cancer diagnoses in double heterozygous mutation carriers was more similar to single *BRCA1* mutation carriers than to single *BRCA2* mutation carriers (see Table 3).

Table 3. Average Age of Diagnosis

	BRCA1/*BRCA2* Double Heterozygote (N=196)	*BRCA1* Single Mutation (N=1000)	*BRCA2* Single Mutation (N=100)
Cancer	**Average, Range of Dx (years)**		
Single Breast	42.7, (21 – 74)	42, (19 – 71)	45.4, (24 – 83)
Multiple Breast*	42.4, (29 – 66)	40.5, (22 – 63)	45.4, (24 – 83)
Single Breast & Ovary	Breast: 51.9, (42 – 63) Ovarian: 56, (38 – 67)	Breast: 49.1, (34 – 79) Ovarian: 55.3, (34 – 81)	Breast: 48.5, (24 – 83) Ovarian: 57.6, (38 – 81)
Multiple Breast & Ovary*	Breast: 35, (27 – 41) Ovarian: 56.3, (47 – 62)	Breast: 40.4, (32 – 62) Ovarian: 55.1, (18 – 75)	Breast: 45.4 (24 – 83) Ovarian: 58.1, (38 – 81)
Ovary	51.7, (40 – 62)	50.8, (34 – 75)	56.7, (38 – 81)

*Age of first breast diagnosis was used.

- As expected, based on the testing population and the increased prevalence of the founder mutations in the Ashkenazi Jewish population, the majority of the double heterozygous mutation carriers were of Western/Northern European ancestry and Ashkenazi Jewish ancestry (Table 4).

Table 4. Double Heterozygous Mutation Carriers by Ancestry

Ancestry	% of Patients (N=196)	
Western/Northern Europe	33.2%	(N=65)
Ashkenazi	25.5%	(N=50)
Central/Eastern Europe	6.1%	(N=12)
Latin American /Caribbean	6.1%	(N=12)
Ashkenazi + Other	4.6%	(N=9)
African	3.6%	(N=7)
Asian	3.1%	(N=6)
Multiple Ancestries indicated	3.1%	(N=6)
Neareast / Mideast	1.5%	(N=3)
None Specified	13.3%	(N=26)

- We also determined the expected prevalence of double heterozygous mutation carriers within the Ashkenazi Jewish population using the known prevalence of the founder mutations. If the mutations were completely independent, then up to 1.85%[3] of the founder *BRCA1* DM carriers would have also carried 6174delT (*BRCA1* prevalence multiplied by gen-pop allele frequency of 6174delT). However, in this testing population, we found a prevalence of 1.08%.

CONCLUSIONS

- Overall the personal histories of individuals with both a deleterious *BRCA1* and a deleterious *BRCA2* mutation are similar to those with a single deleterious mutation in either the *BRCA1* or *BRCA2* genes.
- However, when separated out by all breast and all ovarian cancer, there does appear to be a slightly increased incidence of breast cancer.

REFERENCES

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