Predicting Germline Mutations in *BRCA1/2* and Beyond: a Comparison of Women with Single and Multiple Breast Primaries

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Synchronous or metachronous breast primaries are a well-known indication of hereditary breast cancer, particularly within *BRCA1/2* mutation carriers. However, the frequency of gene mutations within this patient group has not been well defined, especially in the setting of multi-gene panel testing (MGPT). We conducted a retrospective review of mutation carrier status in a population of females with breast cancer(s), but no other reported cancer diagnoses, and who had MGPT at a single diagnostic laboratory. Among 31,864 females tested, the following were excluded from analysis: 5389 (17%) had variants of unknown significance (VUS), 133 (0.4%) had moderate risk mutations and 316 (1.0%) had *MUTYH* monoallelic mutations. For the remaining 26,026 females, we evaluated whether mutation status is associated with risk of multiple breast primaries using Fisher's exact test and logistic regression analysis adjusting for age at testing, age at first breast cancer diagnosis, and mutations in other genes. The number of genes analyzed ranged from 5-49, depending on the panel ordered. Gene-specific analyses were limited to with 10 or more mutations in this cohort (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, MRE11A, MUTYH, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D,* and *TP53*).

In this cohort the average age of first breast cancer diagnosis was 47.7 (range 12-95) and the average age of second diagnosis was 56 years (range 17-89). A positive result (pathogenic mutation or variant, likely pathogenic) in any gene was more likely for women with three or more breast cancer primaries (p=0.007) and two or more primaries (p=1.2e-08) than those with one breast primary.

Overall, women with a mutation in any gene were more likely to have multiple primary breast cancers than those without mutations. Specifically, women with mutations in *ATM, BRCA1, CDH1, PALB2, PTEN*, and *TP53* mutations were more likely to have multiple breast primaries than non-carriers of mutations in those genes (table 1).

Our results show that women with multiple breast primaries are more likely to have mutations in some genes than others. Interestingly, all genes with significant odds ratios are well-described and most are known to cause high risk for breast cancer, with the exception of *ATM*. Additional studies are needed to confirm these results and quantify risks for second primary breast cancers. With further work defining the risks of multiple primary breast cancers, this information could be implemented into clinical practice to aid women in risk management following a positive result.

Table 1: Risk of multiple breast primaries in mutation carriers versus non-carriers

	No. (%) with multiple primaries			
Gene	Carrier	Non-carrier	OR (95% CI)	P-value
ATM	55/262 (21%)	2189/15057 (15%)	1.6 (1.1, 2.2)	0.006
BRCA1	100/526 (19%)	3104/24117 (13%)	1.9 (1.5, 2.4)	3.2e-07

CDH1	6/24 (25%)	3338/25016 (13%)	2.8 (1.0, 7.0)	0.04
PALB2	45/218 (21%)	2199/15101 (15%)	1.7 (1.2, 2.4)	0.004
PTEN	7/28 (25%)	3429/25788 (13%)	3.8 (1.5, 8.9)	0.003
TP53	19/96 (20%)	3419/25787 (13%)	2.4 (1.3, 4.0)	0.002