Magnitude of Invasive Breast Cancer Risk Associated with Mutations Detected by Multiple-Gene Germline Sequencing in 95,561 Women

Michael J. Hall, MD, MS[1]; Elisha Hughes, PhD[2]; Elizabeth A. Handorf, PhD[1]; Alexander Gutin, PhD[2]; Brian Morris, BS[2]; Brian Allen, MS[2]; Anne-Renee Hartman, MD[2]; Allison W. Kurian, MD, MSc[3]

[1]Fox Chase Cancer Center, Philadelphia, PA; [2]Myriad Genetics, Inc., Salt Lake City, UT; [3]Stanford University Cancer Institute, Stanford, CA

BACKGROUND

- Risk assessment for hereditary breast cancer has expanded with the use of multi-gene panel testing, approximately doubling the mutation detection rate over *BRCA1* and *BRCA2* testing alone.
- However, there is still uncertainty about the magnitude of breast cancer risk associated with mutations in less widely tested genes currently included in panels.
- Recommendations for enhanced breast screening and/or preventative surgeries are based on a patient's level of cancer risk as it relates to her genetic status.
- Most studies to estimate gene-specific breast cancer risk are under-powered.

OBJECTIVE

- The breast cancer risk associated with 25 genes included in one multi-gene hereditary cancer panel was estimated by multivariable logistic regression analysis using data from a commercial testing laboratory.

METHODS

PATIENTS

- We studied 95,561 women who underwent clinical testing for hereditary cancer risk with a 25-gene panel between September 2013 and September 2015.
- This cohort excludes women who did not have complete information on the test requisition form (TRF), underwent panel testing after testing negative with a different genetic test at the same laboratory, were identified as carrying a potentially somatic mutation.
- All clinical information was collected on the TRF.

GENETIC TESTING

- The 25 gene panel includes *ATM*, *APC*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A (p16INK4a and p14ARF)*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PTEN*, *PMS2*, *RAD51C, RAD51D*, *SMAD4*, *STK11*, *TP53*.
- Sequencing and large rearrangement (LR) analysis was performed for all genes on the panel except *EPCAM*, for which only LR analysis in the terminal exons is performed.
- Pathogenic variants are those with a laboratory classification of Deleterious or Suspected Deleterious (Eggington et al. *Clin Genet*. 2014;86:229-237).

STATISTICAL METHODS

- Relative breast cancer risk (association between PVs and personal history of ductal invasive breast cancer) was estimated by odds ratios from multivariable logistic regression models.
- Breast cancer status was the dependent variable. Independent variables were age, personal/family cancer history, and self-identified ancestry/ethnicity.
- Confidence intervals (CI) and p-values were based on Wald statistics. All p-values were reported as two-sided. No adjustments were made for multiple testing.
- Odds ratios with 95% CI excluding 1.0 were considered significant.
- Based on limited variant screening, *EPCAM* was excluded from analysis.

RESULTS

- Patient demographics and clinical characteristics are summarized in Table 1.
  - 28% of patients had a personal history of breast cancer, and 38% had ≥1 first-degree relative with breast cancer.

Table 1. Demographics and Clinical Characteristics

Gene	All Patients(%)	BC Cases (%)
All Patients	95,561 (100)	26,384 (28)
Age at Testing		
Range	11-98	18-98
Median	48	55
% ≤ 50	57	38
Ancestry		
Western/Northern European	54,372 (57)	16,439 (62)
Central/Eastern European	13,134 (14)	2,411 (9)
Latin American/Caribbean	8,915 (9)	2,266 (9)
African	8,829 (9)	2,768 (10)
Native American	3,925 (4)	832 (3)
Asian	3,195 (3)	996 (4)
Ashkenazi	2,211 (2)	407 (2)
Near/Middle Eastern	980 (1)	266 (1)
Family Cancer History		
≥1 FDR with BC	36,389 (38)	9,493 (36)

FDR, first -degree relative; BC, invasive ductal breast cancer

Figure 1. Distribution of pathogenic variants in women with breast cancer (n=2701)

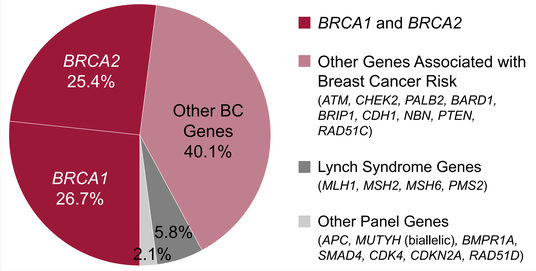


Table 2. Results from multivariate logistic regression models

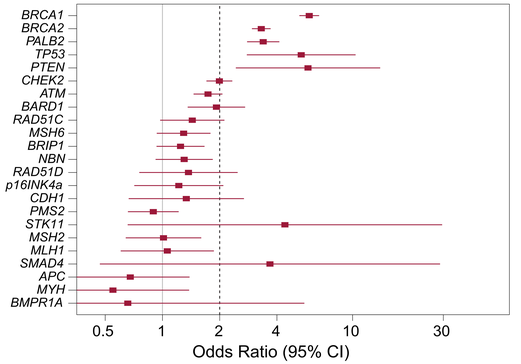
Gene	Odds Ratio	95% CI	p-value
BRCA1	5.91	5.25-6.67	2.2×10^{-186}
PTEN	5.83	2.43-14.0	7.7×10^{-05}
TP53	5.37	2.78-10.4	5.7×10^{-07}
PALB2	3.39	2.79-4.12	2.0×10^{-34}
BRCA2	3.31	2.95-3.71	2.7×10^{-95}
CHEK2	1.99	1.70-2.33	6.8×10^{-18}
BARD1	1.92	1.36-2.72	2.3×10^{-04}
ATM	1.74	1.46-2.07	6.5×10^{-10}
APC	0.68	0.33-1.39	0.29
BMPR1A	0.66	0.08-5.58	0.70
BRIP1	1.24	0.93-1.66	0.14
CDH1	1.34	0.66-2.68	0.42
MLH1	1.06	0.60-1.86	0.84
MSH2	1.01	0.64-1.60	0.96
MSH6	1.29	0.93-1.79	0.12
MUTYH (biallelic)	0.55	0.22-1.38	0.20
NBN	1.30	0.92-1.84	0.14
p16INK4a	1.22	0.71-2.09	0.47
PMS2	0.89	0.66-1.22	0.48
RAD51C	1.43	0.97-2.12	0.069
RAD51D	1.37	0.76-2.49	0.30
SMAD4	3.68	0.47-28.8	0.22
STK11	4.41	0.66-29.6	0.13
*CDH1**	17.7	7.68-40.1	1.4×10^{-11}

*Additional analysis with analogous models to predict lobular breast cancer risk in *CDH1*

NOTE: Odds ratios could not be calculated for *CDK4* or *CDKN2A p14ARF* as no pathogenic variants in these genes were identified in women with breast cancer.

- Among 95,561 women tested, 6,775 pathogenic variants were detected in 6,626 (7%) patients
  - The majority of pathogenic variants occurred in *BRCA1/2* (44.4%) or other genes associated with breast cancer risk (40.6%).
- Among all women with a personal diagnosis of breast cancer, 10% (2,701) had at least one pathogenic variant (Figure 1).
  - 52.0% of pathogenic variants were in *BRCA1/2*.
  - 40.1% of pathogenic variants were in other genes associated with breast cancer risk.

Figure 2. Odds ratios and 95% CIs from multivariate logistic regression models of breast cancer associations



Odds ratios could not be calculated for *CDK4* or *CDKN2A p14ARF* as no pathogenic variants in these genes were identified in women with breast cancer.

- Multivariate logistic regression models indicated significant breast cancer risk associations for *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *ATM*, *TP53*, *PTEN* and *BARD1* (Table 2 and Figure 2).
  - Analogous models were used to predict lobular breast cancer risk and showed significant associations for *CDH1* (Table 2).
- Relative risk estimates for breast cancer for these genes ranged from approximately 2-fold (*ATM*, *CHEK2*, *BARD1*) to 6-fold (*BRCA1*, *PTEN*).

CONCLUSIONS

- Among nearly 100,000 women tested clinically for hereditary cancer risk, multiple-gene panel testing identified a wide spectrum of PVs in genes associated with breast cancer risk, approximately half of which were in genes other than *BRCA1* or *BRCA2*.
- Eight genes were associated with a 2- to 6-fold increase in breast cancer risk.
- These results inform the estimation of BC risk for mutation carriers of diverse high-risk genes.

Contact Michael Hall at Michael.Hall@fccc.edu with questions

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