Polygenic Breast Cancer Risk Modification in Carriers of High and Intermediate Risk Gene Mutations

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BACKGROUND

- Recent studies have demonstrated that the accuracy of breast cancer risk assessment models for women without pathogenic variants (PVs) in breast cancer susceptibility genes can be significantly improved by incorporating a validated polygenic risk score (PRS). However, few studies have examined the extent to which a PRS can also modify risk in the subset of women who do carry such PVs.
- In a recent study¹, a 77-SNP PRS developed in large European populations² stratified breast cancer risk for carriers of the common *CHEK2* founder mutation 1100delC with an effect size similar to that observed for non-carriers of this PV. Subsequently, several groups have suggested that risk estimates for carriers of PVs in other breast cancer susceptibility genes can be modified using published effect estimates from non-carriers.
- In another recent study³, a similar polygenic score showed reduced effectiveness in *BRCA1* and *BRCA2* carriers compared to non-carriers.
- The validation of models utilizing a PRS to modify breast cancer risk estimates for women who carry PVs in both high and moderate risk genes would allow for more precise risk estimates and individually tailored care.
- Here, we performed such a validation study, using a previously described 86-SNP PRS³, for the genes BRCA1, BRCA2, ATM, CHEK2 and PALB2. We found that this PRS, previously validated for women without PVs in these five genes, also significantly improves the precision of risk estimates in carriers of PVs.

METHODS

COHORT

- This IRB-approved study included 152,012 women of European ancestry who were tested clinically for hereditary cancer risk with a multi-gene panel.
- The 86-SNP PRS was evaluated separately for carriers of PVs in BRCA1 (N=2,249), BRCA2 (N=2,638), CHEK2 (N=2,564), ATM (N=1,445) and PALB2 (N=906), and for non-carriers (N=141,160).
- Clinical information was obtained from test requisition forms.

STATISTICAL ANALYSIS

- Multivariable logistic regression was used to examine the association of 86-SNP PRS with invasive breast cancer after accounting for age and family cancer history.
- Effect sizes, expressed as standardized odds ratios (ORs) with 95% confidence intervals (CIs), were assessed for carriers of each gene and for non-carriers.

References: 1. Muranen T, et al. *Genetics in Medicine* (2017); 2. Mavaddat N, et al. *JNCI* (2015); 3. Kuchenbaecker K, et al. *JNCI* (2017); 4. Hughes E, et al. *SABCS* (2017 presentation)

Table 1. Clinical characteristics and biodata of clinical cohort.

Gene	Non- Carriers	BRCA1	BRCA2	ATM	CHEK2	PALB2						
Total Patients	141,160	2,249	2,638	1,445	2,564	906						
Age at Hereditary Cancer Testing, Years												
Range	18 - 84	18 - 84	18 - 84	18 - 84	18 - 84	18 - 82						
Median	48	43	47	49	48	51						
Breast Cancer History, N (%)												
Personal BC	28,928 (20)	828 (37)	897 (34)	486 (34)	914 (36)	401 (44)						
≥1 FDR or SDR	FDR or SDR 100,216 (71)		2,003 (76)	1,101 (76)	1,972 (77)	720 (79)						
Ancestry, N (%)												
AJ	2,924 (2)	69 (3)	59 (2)	16 (1)	24 (1)	8 (1)						
W/NH	134,819 (96)	2,115 (94)	2,504 (95)	1,404 (97)	2,504 (98)	886 (98)						
AJ and W/NH	3,417 (2)	65 (3)	75 (3)	25 (2)	36 (1)	12 (1)						
Δ L Ashkanazi Jawish: BC Invasiva breast cancer: FDR First-degree relative: SDR Second-degree relative: W/NH White/Non Hispanic												

AJ, Ashkenazi Jewish; BC, Invasive breast cancer; FDR, First-degree relative; SDR, Second-degree relative; W/NH, White/Non Hispanic

- The 86-SNP PRS was strongly associated with breast cancer risk in *BRCA1*, *BRCA2*, *CHEK2*, *ATM* and *PALB2* carrier populations (p < 10⁻⁴).
- Risk modification in *CHEK2* carriers was consistent with that observed in non-carriers (Figure 1).
- CHEK2 carriers in the highest 86-SNP PRS tercile had approximately 1.6-fold higher risk than the middle tercile, and the lowest tercile had risk lowered by a factor of 0.59 (Table 2).
- We observed reduced modification similar to existing literature for carriers of BRCA1 and BRCA2 (Figure 1).
- Odds ratios for ATM and PALB2
 had wide confidence intervals that
 overlapped those for the other carrier
 populations (Figure 1).
- Modified risk estimates were comparable to population average for women with PVs in ATM or CHEK2 who were in the lowest 86-SNP PRS percentile. In contrast, moderate risk PV carriers in the highest 86-SNP PRS percentiles were similar to BRCA1/2 carriers (Table 3, Figure 2).

Table 3. Estimated lifetime breast cancer risk to age 80 and modification by an 86-SNP PRS.

	Gene- Based	86-SNP PRS Adjusted Risk							
Gene	Risk (%)	Median (%)	Range (%)						
Non- Carriers	12.7*	12.9	2.4–62						
BRCA1	73.5**	73.8	53-92						
BRCA2	73.8**	74.2	51–94						
ATM	28.2**	29.0	13–58						
CHEK2	22.1**	23.0	6.6–71						
PALB2	50.1**	50.3	26–79						
*General popula	ation risk from	SEER data, 201	3–2015						

*General population risk from SEER data, 2013–2015
**Lee A, et al., *Genetics in Medicine* (2016) for *BRCA1*, *BRCA2*, *PALB2*, and *ATM PVs*; Lee A, et al. *Genetics in Medicine* (2019) for *CHEK2* 1100delC PVs.

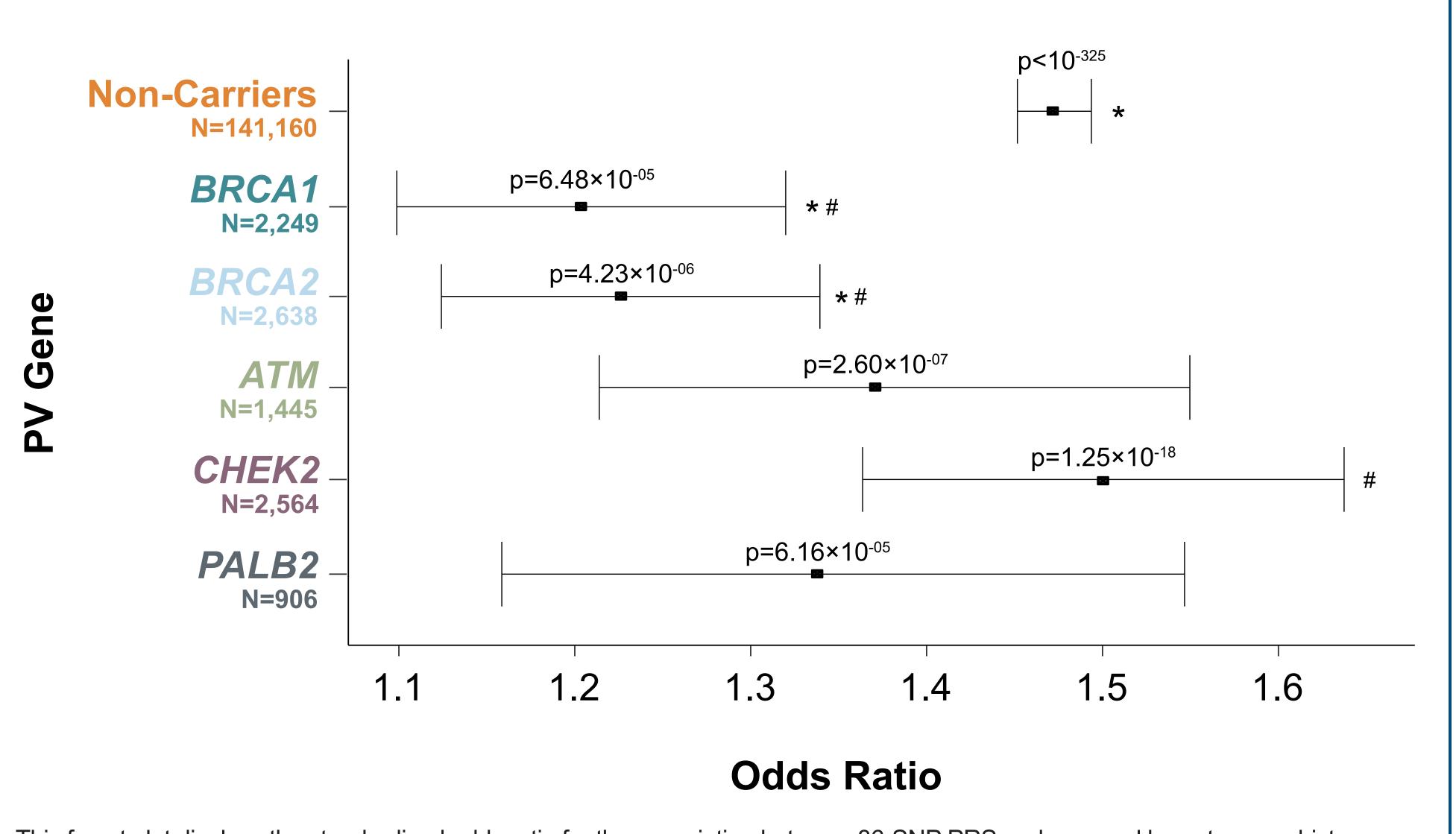
RESULTS

Table 2. Odds ratios for developing breast cancer by percentile of 86-SNP PRS & by carrier status for PV in a breast cancer associated gene.

86-SNP	Non-Carriers		BRCA1		BRCA2		ATM			CHEK2			PALB2					
86-SNP PRS Percentile	N	OR (95% CI)	p-value	N	OR (95% CI)	p-value	N	OR (95% CI)	p-value	N	OR (95% CI)	p-value	N	OR (95% CI)	p-value	N	OR (95% CI)	p-value
≤33	46,583	0.68 (0.66–0.71)	2.11×10 ⁻⁹⁰	742	0.87 (0.7–1.1)	0.25	871	0.74 (0.6–0.92)	0.0077	477	0.61 (0.45–0.82)	0.0013	846	0.61 (0.49–0.77)	3.19×10 ⁻⁵	299	0.68 (0.47–0.98)	0.039
>33–≤66ª	46,582	1		742	1		870	1		477	1		846	1		299	1	
>66	47,995	1.59 (1.53–1.64)	9.28×10 ⁻¹⁶⁵	765	1.31 (1.05–1.64)	0.017	897	1.16 (0.94–1.43)	0.17	491	1.23 (0.93–1.64)	0.15	872	1.59 (1.29–1.97)	2.11×10 ⁻⁵	308	1.37 (0.96–1.95)	0.085

^aThe middle percentile was used as the referent; p-values are for the difference in effect size between the percentile of the 86-SNP PRS and the referent group.

Figure 1. Standardized odds ratios for association between 86-SNP PRS and personal breast cancer history for carriers of each gene and non-carriers.



This forest plot displays the standardized odds ratio for the association between 86-SNP PRS and personal breast cancer history along with 95% confidence intervals for carriers of each gene and non-carriers.

*denotes a significant difference (p < 1×10⁻⁴) between non-carriers and individuals with a PV in *BRCA1/BRCA2*.

#denotes a significant difference (p < .01) between individuals with *CHEK2* PVs and those with a PV in *BRCA1/2*.

associated genes, as modified by 86-SNP PRS.

Non-Carriers

BRCA1

CHEK2 ATM

PALB2

BRCA2

Breast Cancer Risk by Age 80 (%)

Figure 2. Lifetime breast cancer risk for carriers of PVs in breast cancer

Probability density function against absolute risk estimates by age 80, shaded by gene with a PV.

Baseline gene-specific risk from Lee A, et al. *Genetics in Medicine* (2016) and Lee A, et al. *Genetics in Medicine* (2019).

Baseline risk for non-carriers was obtained using SEER 2013-2015 lifetime risk data for individuals with white ancestry.

DISCUSSION

- The 86-SNP PRS significantly modifies risk for carriers of *BRCA1*, *BRCA2*, *CHEK2*, *ATM* and *PALB2* PVs albeit with apparently different effect sizes.
- These results indicate that risk estimates employing polygenic scores may need to be derived separately for each gene.
- Given the substantial risks conferred by *BRCA1* and *BRCA2* at all PRS levels, it may be that the greatest clinical utility for PRS risk-modification lies with *CHEK2*, *ATM* and *PALB2*.
- In CHEK2 carriers, we observed strong polygenic modification similar to that achieved for non-carriers.
- For *ATM* and *PALB2*, larger studies are needed to refine polygenic effect size estimates.
- Comprehensive risk assessment combining an 86-SNP PRS with risk factors may improve the accuracy of risk estimates and facilitate decision-making for women with PVs in moderate penetrance genes.

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