Polygenic risk is independent from the risk conferred by pathogenic variants in 12 known breast cancer genes

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Introduction

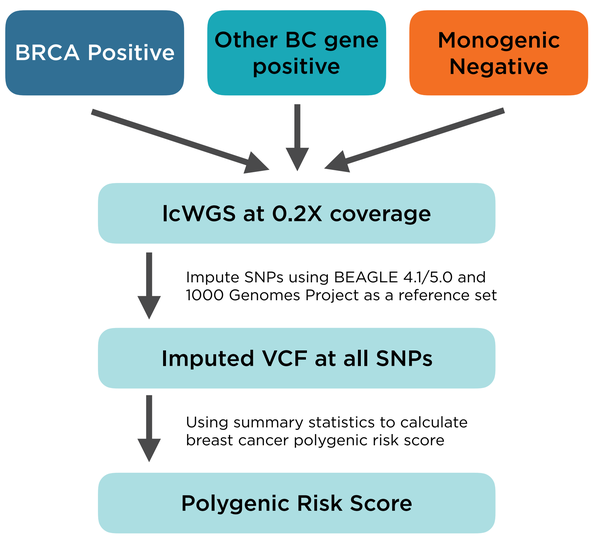
Breast cancer is the most common cancer among women, accounting for nearly 30% of newly diagnosed cancers in women in the United States during 2017. Approximately 5-10% of female breast cancer is associated with germline pathogenic or likely pathogenic (P/LP) variants, the majority of which are inherited in an autosomal dominant manner. While this monogenic risk is often predictive of age of onset and lifetime risk, it does not explain all the phenotypic variability observed, especially within the same family.

Recent studies have demonstrated that polygenic risk scores (PRS) can be used to stratify the risk for breast cancer in the general population, with a 3-fold or higher increase in risk for individuals of European genetic ancestry who are in the top 5% of the score[1]. However, whether this holds true in individuals with P/LP variants is still unknown. To investigate the interaction between polygenic risk and monogenic risk for breast cancer, we calculated a previously published PRS for breast cancer[1] in 11,521 unrelated females with European genetic ancestry. Here, we assess breast cancer risk using a logistic regression model adjusted for age and for gene in individuals who carry a P/LP variant. Self-reported personal history of breast cancer diagnosis was used as the outcome.

Methods

The study design is summarized in Figure 1 and described in detail below.

Figure 1. Study Design and PRS Analysis Workflow



The cohort included DNA samples from 11,521 individuals whose healthcare provider had ordered a Color multi-gene panel test and who had given informed consent to have their de-identified information and sample used in anonymized studies. Demographics are provided in Table 1. All individuals 1) had 85% or greater European genetic ancestry calculated using fastNGSadmix[2] using the 1000 Genomes Project as a reference set, 2) identified as 'Caucasian', and 3) provided sufficient health history. Of the 11,523 individuals, 700 had a P/LP variant in *BRCA1* or *BRCA2* (hereafter referred to as 'BRCA positive'), 823 had a P/LP variant in *TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1,* or *BRIP1* (hereafter referred to as 'other BC gene positive'), and 9998 individuals did not have a P/LP in any of these 12 genes (hereafter referred to as 'monogenic negative'). All phenotypic information was self-reported by the individual through an online, interactive health history tool. BC, breast cancer.

Laboratory procedures were performed at the Color laboratory. DNA was extracted from blood or saliva samples and sequenced using NextSeq 500/550 or NovaSeq 6000 instrument. All samples had at least 0.2X low coverage whole genome sequencing (lcWGS) data available. lcWGS data were imputed to a set of 21,770,397 autosomal single nucleotide polymorphism (SNP) and insertion and deletion (indel) sites from the 1000 Genomes Project. All loci in the breast cancer PRS[1] were included in the imputation, and the raw breast cancer PRS was normalized using the population mean and standard deviation.

Results

Table 1. Cohort demographics details

A total of 1523 females had a P/LP variant in one of 12 genes associated with hereditary breast cancer.

		BRCA Positive*	Other BC Gene Positive†	Monogenic Negative
Number of Individuals		700 (6.1%)	823 (7.1%)	9998 (86.8%)
Personal History of BC	Yes	109 (15.6%)	173 (21.0%)	837 (8.4%)
	No	591 (84.4%)	650 (79.0%)	9161 (91.6%)
Age (Years)	18-30	144 (20.6%)	54 (6.6%)	874 (8.7%)
	31-45	250 (35.7%)	252 (30.6%)	3245 (32.5%)
	46-60	195 (27.9%)	276 (33.5%)	3714 (37.1%)
	60+	111 (15.9%)	241 (29.3%)	2165 (21.7%)

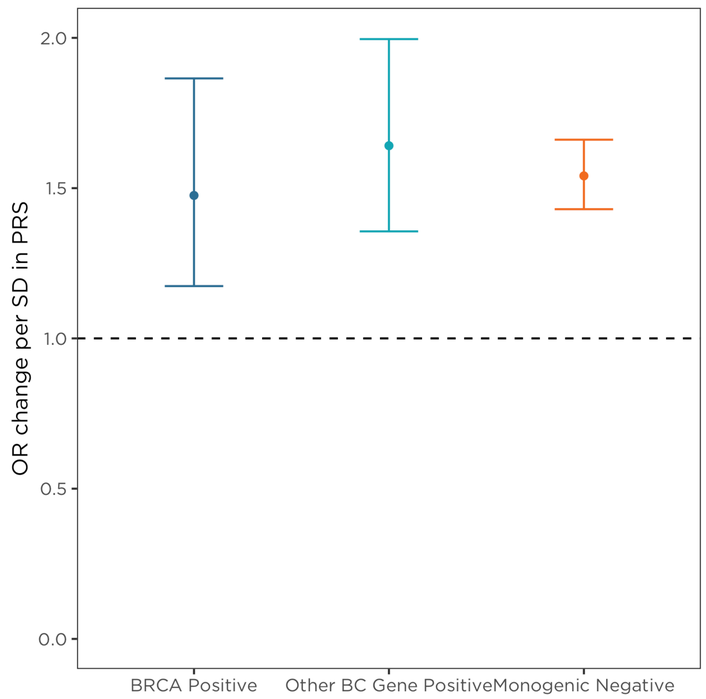
*BRCA positive includes P/LP variants in *BRCA1* and *BRCA2.*
†Other BC gene positive includes pathogenic variants in *TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1,* and *BRIP1.*
BC, breast cancer.

Figure 2: Polygenic risk scores stratify breast cancer prevalence

It is well-established that the penetrance of P/LP variants differs between genes associated with hereditary breast cancer. To determine the effect of polygenic risk in individuals with variants in the highest penetrance genes, we restricted our next analysis to 700 females with a P/LP variant in *BRCA1* or *BRCA2.* We found that high PRS increases the rate of breast cancer (OR 1.48 per SD, CI: 1.17-1.87, p=0.0096) after adjusting for age and *BRCA1* and *BRCA2* positivity.

We found a similar OR increase of 1.57 (CI: 1.36 - 1.82, p=1.90 x 10^{-9}) in the 823 individuals who carried a P/LP variant in *TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1,* and *BRIP1.*

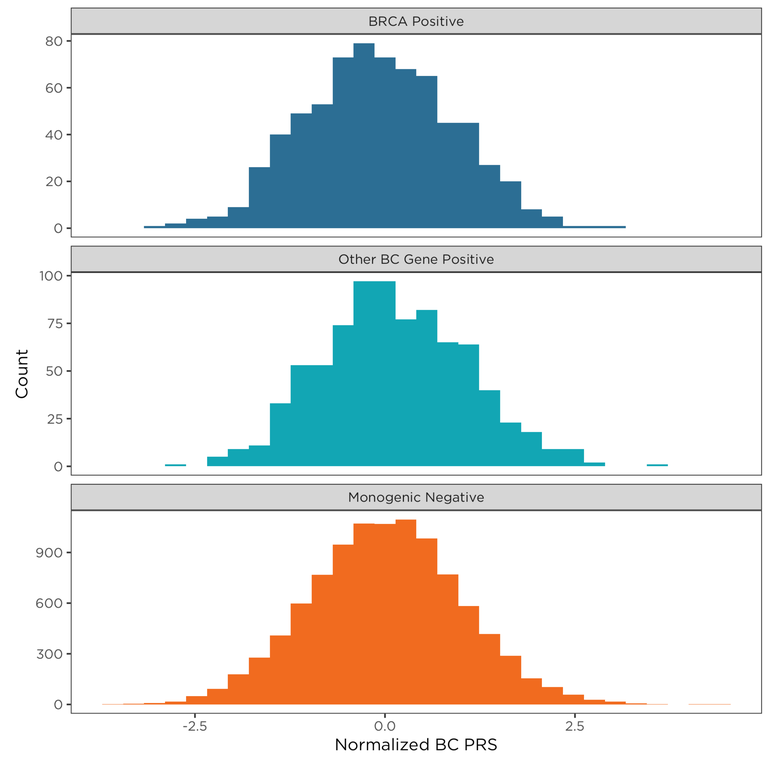
In 9998 female individuals who did not carry a known P/LP variant, the OR increase in breast cancer risk per SD of PRS was 1.54 (CI: 1.43 - 1.66, p<10^{-16}), which is consistent with results from other studies[3,4].



OR, odds ratio. SD, standard deviation.

Figure 3: Polygenic risk score is independent of monogenic carrier status

While the baseline risk of breast cancer for each of these three subpopulations (BRCA positive, other BC gene positive, and monogenic negative) is different, the odds increase in risk associated with the PRS is the same. We found no significant difference in the distribution of raw PRS between groups (KS test p = 0.06 vs. BRCA positive, p = 0.69 vs. other BC gene positive).



When we included both monogenic and polygenic risk in a joint model of 11,521 individuals, we found that monogenic variants were associated with an odds increase of 2.80 (CI: 2.37 - 3.31, p<10^{-16}), and the PRS again had a similar odds increase of 1.54 per SD (CI: 1.43 - 1.66, p<10^{-16}). We observed no interaction between monogenic variants and PRS (p=0.99), suggesting independence between these two risk factors.

Conclusions

- In this large clinical test population, we demonstrate that polygenic risk is independent from the risk conferred by P/LP variants in known breast cancer genes and that combining monogenic and polygenic risk results in improved risk stratification for breast cancer.
- Our work suggests polygenic risk that may help to explain the phenotypic variability in individuals with the same P/LP variant.
- While more in depth studies of the clinical utility of polygenic testing are warranted, polygenic risk could be an important additional risk factor when considering treatment and screening plans in all individuals, including those with high-to-moderate penetrance genes.
- Taken together, these data demonstrate that monogenic and polygenic risk are independent risk factors for breast cancer and that individuals with P/LP variants who have a high PRS have an increased rate of breast cancer.

References

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