

Common variant genetic background modifies risk of breast cancer among carriers of pathogenic germline risk variants

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Introduction

DNA sequencing of individuals affected by breast cancer reveals a pathogenic or likely pathogenic (P/LP) variant in 5-10% of individuals. While carriers of a P/LP variant have a several-fold increased risk, many do not develop cancer. The causes of this incomplete penetrance are currently unknown. Here, we demonstrate that common variant background, assessed in the form of a genome-wide polygenic score (GPS), modifies the penetrance of P/LP variants for risk of breast cancer.

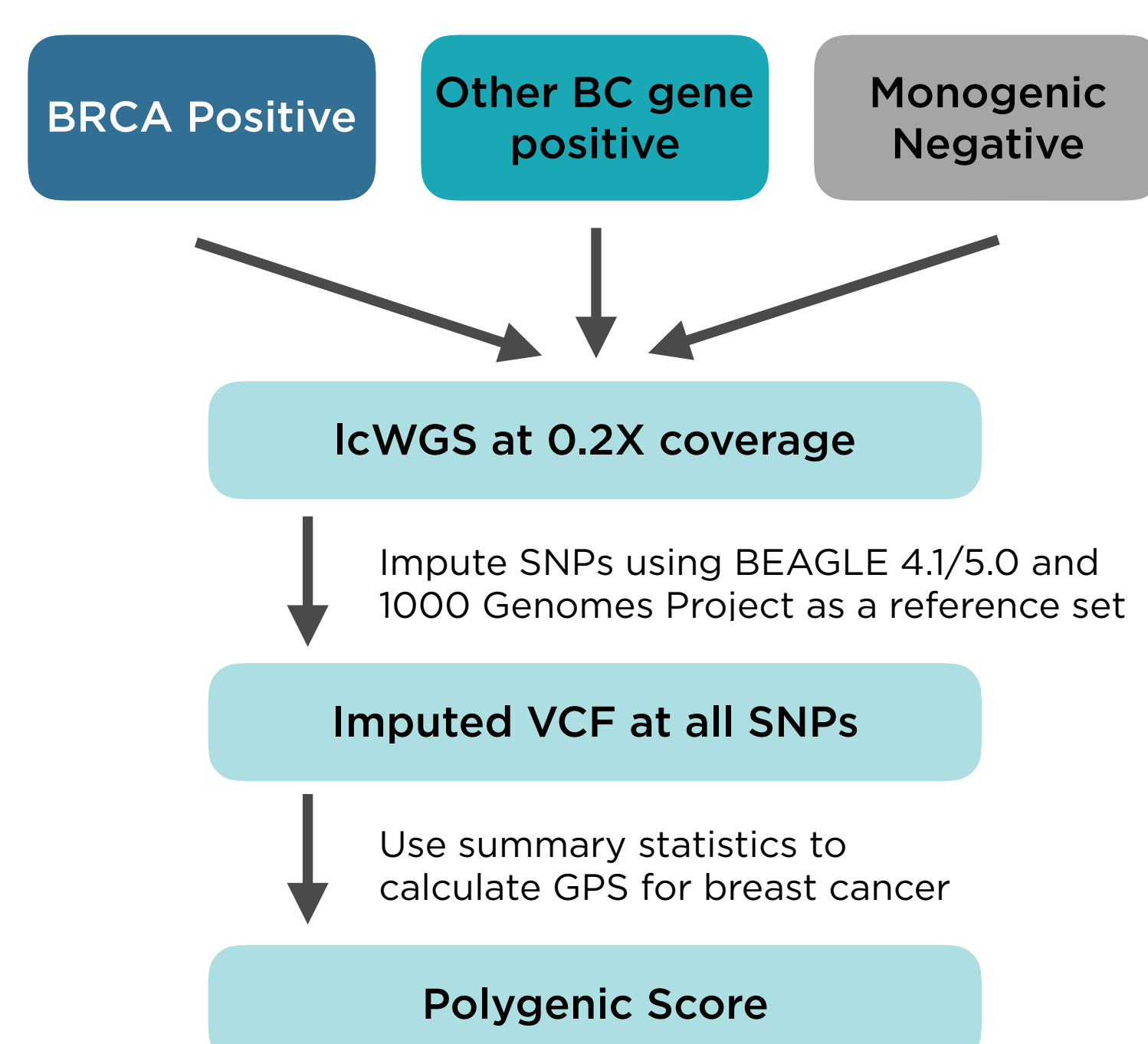
Recent studies have demonstrated that genome-wide polygenic score (GPS) can be used to stratify the risk for breast cancer in the general population, with a 3-fold or higher increase in risk for individuals of European genetic ancestry who are in the top 5% of the score^{1,2}. However, whether this holds 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 GPS for breast cancer¹ in 20,031 unrelated females. Here, we assess breast cancer risk using a logistic regression model adjusted for age at genetic testing 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. The cohort included DNA samples from

- 20,031 individuals whose healthcare provider 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 and
- 50,000 individuals in UK Biobank with exome sequencing data.

Figure 1. Study Design and GPS Calculation



Odds ratios were estimated using a logistic regression model with age, sex, and the first four principal components of ancestry as covariates. For breast cancer, analysis was limited to females only, and sex was not included in the model.

Conclusions

- Polygenic risk is independent from the risk conferred by P/LP variants in known breast cancer genes and 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.
- Polygenic scores could be an important additional risk factor when considering treatment and screening plans in all individuals, including those with P/LP variants in high-to-moderate penetrance genes.

Results

Table 1. Cohort demographics details

A total of 1517 females had a P/LP variant in one of 12 genes associated with hereditary breast cancer.

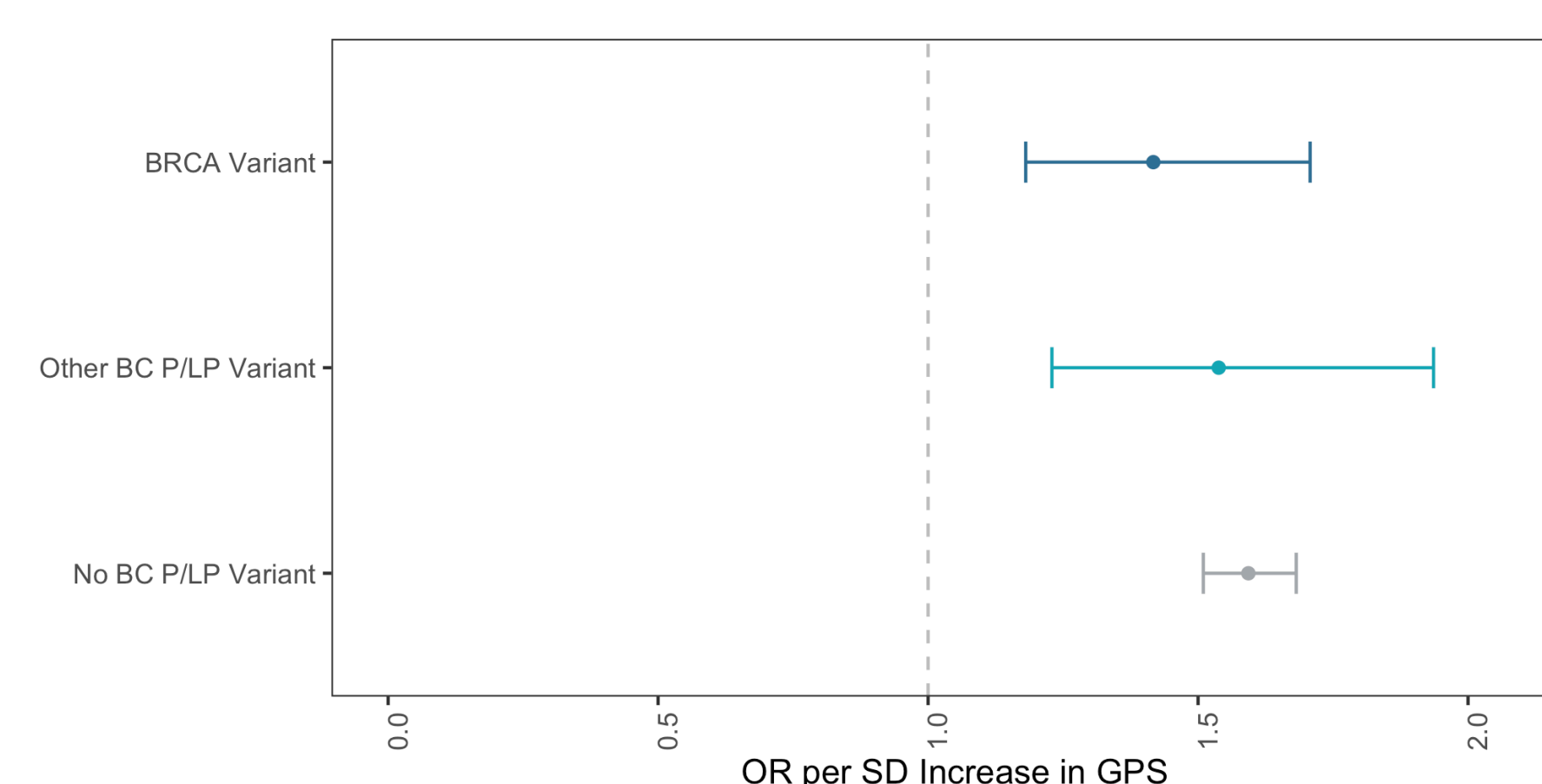
	BRCA Positive*	Other BC Gene Positive†	Monogenic Negative	
Total Individuals	850 (4.2%)	667 (3.3%)	18,514 (92.4%)	
Personal History of BC	Yes	176 (20.7%)	152 (22.7%)	1755 (9.5%)
	No	674 (79.3%)	515 (77.3%)	16,759 (90.5%)
Age (Years)	18-30	155 (18.2%)	60 (9.0%)	2127 (11.4%)
	30-45	313 (36.8%)	218 (32.7%)	6291 (34.0%)
	45-60	248 (29.1%)	219 (32.8%)	6434 (34.8%)
	60	134 (15.7%)	170 (25.5%)	3662 (19.8%)

*BRCA positive includes P/LP variants in *BRCA1* and *BRCA2*.

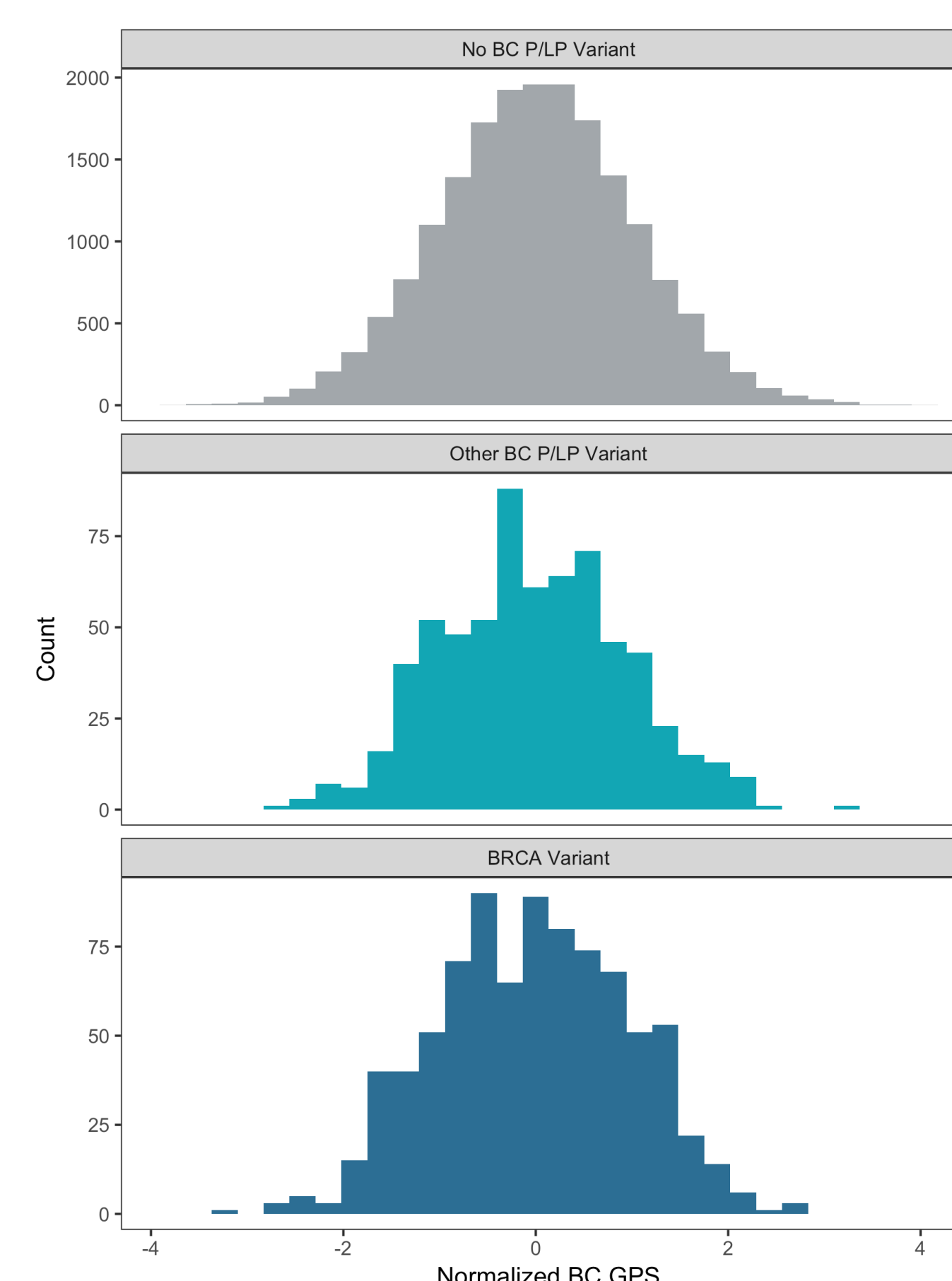
†Other BC gene positive includes pathogenic variants in *TP53*, *PTEN*, *STK11*, *CDH1*, *PALB2*, *CHEK2*, *ATM*, *NBN*, *BARD1*, and *BRIP1*. BC, breast cancer.

Figure 3. GPS stratifies breast cancer prevalence for carriers and noncarriers similarly

(A) A high GPS increased the rate of breast cancer in BRCA positive females (n = 850, OR 1.42 per SD, CI: 1.18 - 1.71, p = 0.0096), in other BC gene positive females (n = 667, OR 1.54 per SD, CI: 1.23 - 1.94, p=1.90 x 10⁻⁹), and in monogenic negative females (n = 18,514, OR 1.59 per SD, CI: 1.51 - 1.68, p<10⁻¹⁶), which is consistent with results from other studies^{3,4}.



(B) While the baseline risk of breast cancer for each of these three subpopulations is different, the odds increase in risk associated with the GPS is the same. There was also no significant difference in the distribution of raw GPS between groups (KS test p = 0.06 vs. BRCA positive, p = 0.69 vs. other BC gene positive).



References

- Mavaddat N, Michailidou K, Dennis J, et al. *Am J Hum Genet.* 2019.
- Khera AV, Chaffin M, Aragam KG, et al. *Nat Genet.* 2018.
- Li H, Feng B, Miron A, et al. *Genet Med.* 2017.

Figure 2. GPS stratifies breast cancer prevalence in noncarriers

GPS for breast cancer stratifies individuals based on the reported prevalence of breast cancer (n = 18,514 individuals, by GPS quantile).

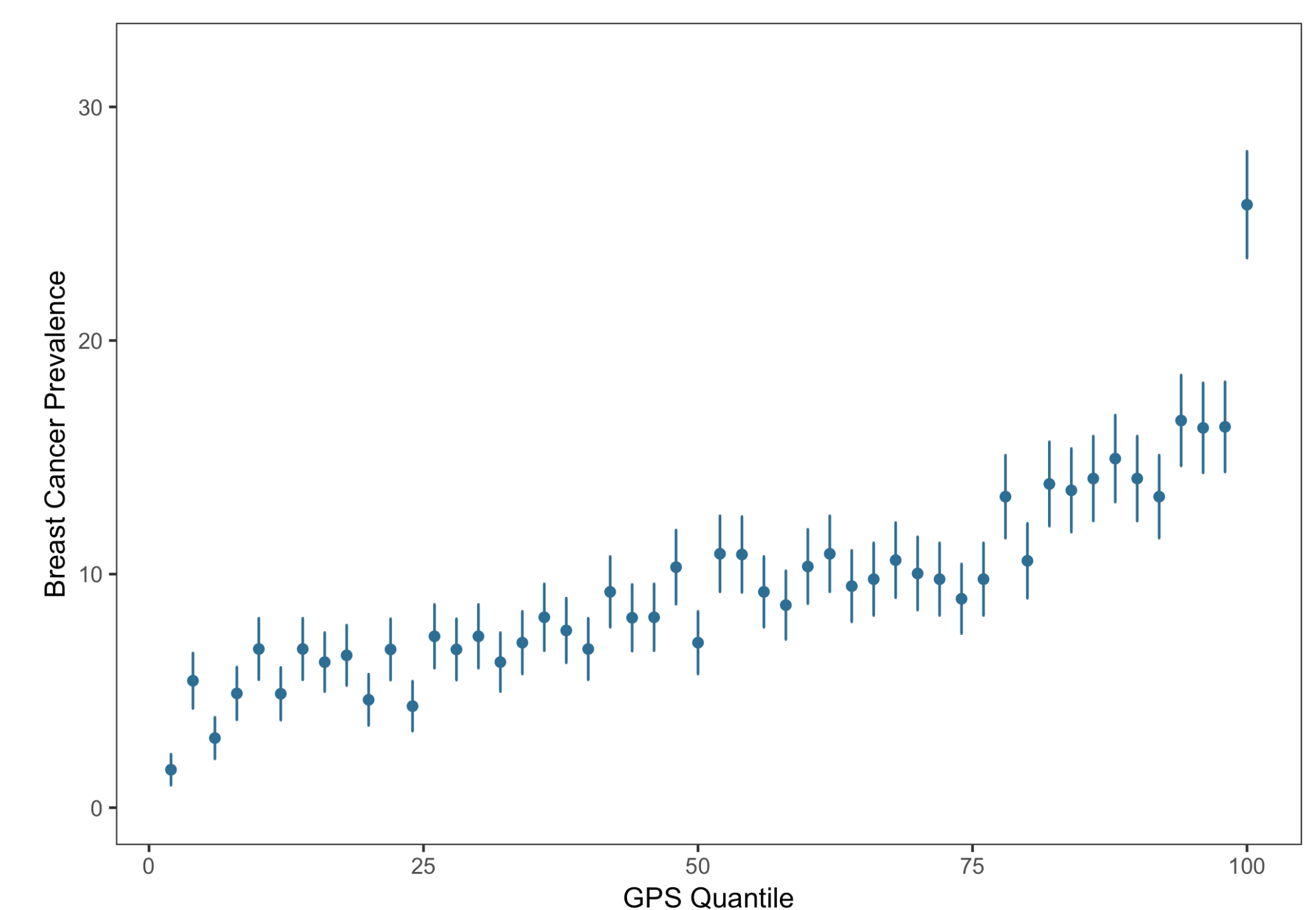


Figure 4. Observed risk levels for carriers and noncarriers with different GPS demonstrate additive risk effect

Individuals with a P/LP variant and a high GPS (defined as 1 SD or more above the mean) have a significantly higher risk for breast cancer, especially compared to individuals with a P/LP variant and a low GPS (defined as 1 SD below the mean).

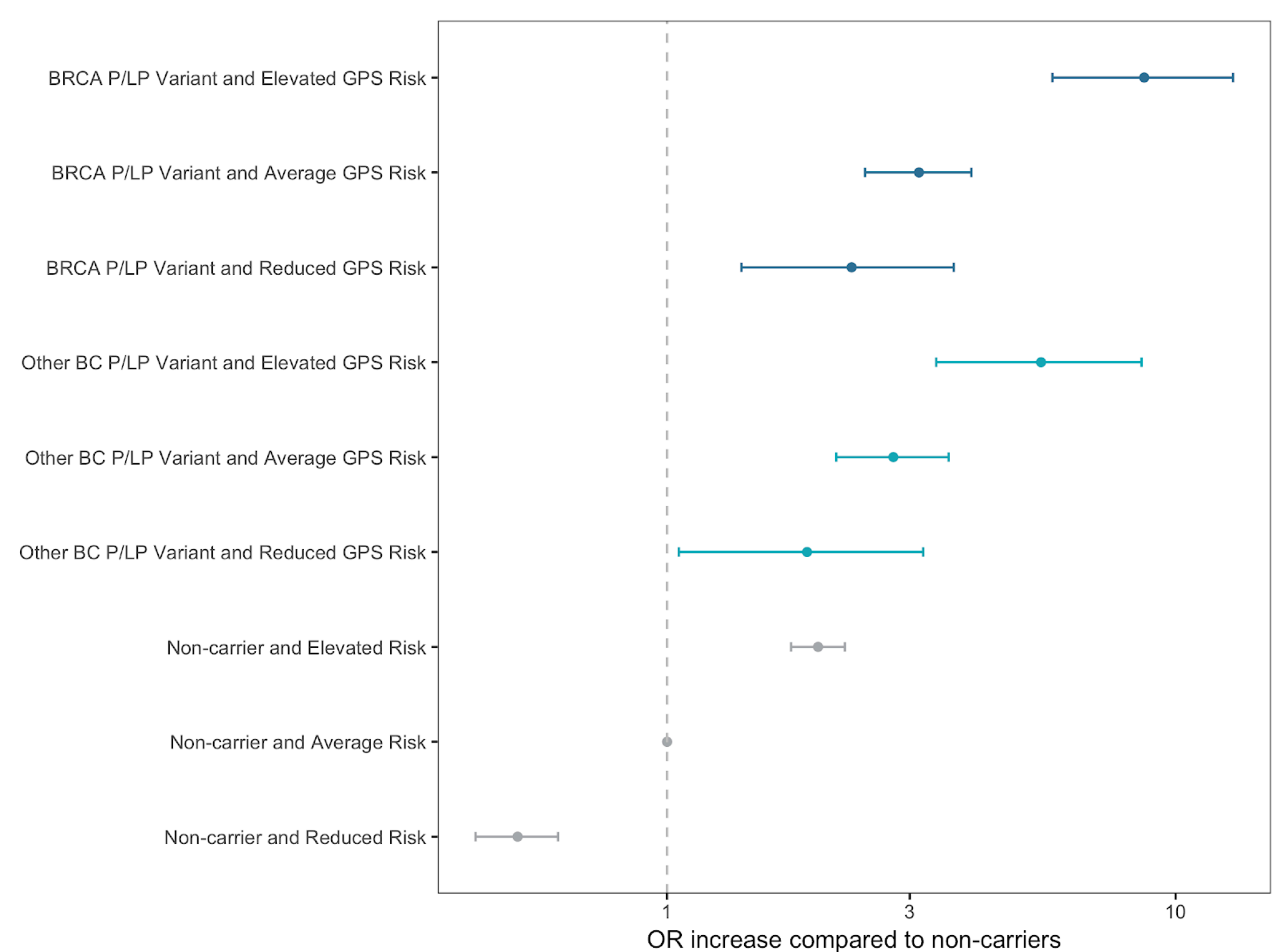


Figure 5. Modeling the disease risk increases across the CDC Tier 1 genomic applications

Predicted OR of disease in each percentile (dots) of the polygenic score distribution for UKBiobank carriers (blue) and noncarriers (brown) of (A) familial hypercholesterolemia variants, (B) BRCA1/2 variants, and (C) colorectal cancer variants (n = 49,738) and for Color carriers (blue) and noncarriers (brown) of (D) breast cancer (n = 19,364).

