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Title: Clinical utility of 99 breast cancer polygenic risk scores (PRSs) in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE)

Background: Female childhood cancer survivors are at high risk for developing subsequent breast cancer (BC). The St. Jude Survivorship Portal, an open-access online survivorship data resource (https://survivorship.stjude.cloud), now includes 3271 PRSs for 541 traits from the PGS Catalog. For a single phenotype, there may be many PRSs, each reflecting different genome-wide association study (GWAS) sample sizes and PRS construction methods. In this study, we systematically evaluated 99 PRSs developed for primary BC for their ability to inform clinical risk stratification for subsequent BC.

Methods: Analyses were limited to the 99 general population PRSs developed for invasive or overall BC. Data for 5-year female survivors of European ancestry (EA) and African ancestry (AA) from CCSS and SJLIFE were analyzed, with PRSs computed under a uniform protocol using whole-genome sequencing or imputed array-based genotype data and pathology-ascertained breast subsequent neoplasms. Ancestry-specific hazard ratios (HRs) for PRSs (per one standard-deviation increase) were estimated with Cox regression using age as the time scale and adjusted for ancestry principal components, batch, chest radiotherapy (RT) and anthracycline doses. To validate a PRS association with HR=1.3, statistical power was 99% in EA survivors and 11% in AA survivors. PRS-RT interactions assessed whether PRSs modified risks conferred by chest RT dose.

Results: Analyses included 4689 EA (292 BCs) and 445 AA (9 BCs) survivors. Median attained age was 39 (IQR 31-47) and 31 (IQR 25-41) years for EA and AA survivors, respectively. Overall, 21% of EA and 13% of AA survivors were treated with chest RT. We observed wide variability in BC PRS effect sizes (Figure): in EA survivors, 86% of PRSs (HR median 1.27, range 1.04-2.17) were associated with BC ($P<0.05$); in AA survivors, 29% were associated (HR median 1.74, range 0.53-13.78). In AA survivors, 43% of the 7 PRSs from multi-ancestry/non-EA GWAS were validated (vs. EA GWAS: 28%). Both GWAS sample size and PRS development methods were associated with HR magnitudes in EA survivors ($P<0.05$). While no PRS-RT interactions were statistically significant in EA survivors, all 16 BC PRSs with differences ≥20% in HR estimates by chest RT dose had a higher HR estimate for those treated with ≤10 Gy, suggesting higher chest RT dose can mask BC polygenic risk. The BC PRS with the largest effect size and $P<5x10^{-8}$ in EA survivors (HR 1.61, 95% CI 1.35-1.90) was from a GWAS with N~229K (~123K cases) and developed with a Bayesian method (LDPred, ~6.4 million variants). For comparison, a widely-studied BC PRS with 313 variants showed a weaker association (HR 1.13, 95% CI 1.00-1.28).

Conclusions: Among the 99 BC PRSs in the Portal, there is wide variation in their methodologic characteristics and effect sizes among childhood cancer survivors. Careful consideration of available BC PRSs is required when utilizing them for subsequent BC risk stratification.

Figure: HR and 95% CI for each breast cancer PRS (per SD increase) among female EA survivors in CCSS and SJLIFE annotated by methodology and GWAS sample size.