Title: Inherited genetic susceptibility of basal cell carcinoma (BCC) and its contribution to risk prediction among long-term survivors of childhood cancer: a St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS) report

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Background: Radiation therapy (RT) and host genetic predisposition are important risk factors for BCC among survivors of childhood cancer. However, the contribution of known genetic risk factors, including common variants summarized as polygenic risk scores (PRSs) and rare pathogenic/likely pathogenic (P/LP) variants, is unknown.

Methods: Analyses used whole-genome/-exome sequencing (WGS/WES) and imputed array-based genotype data and confirmed BCCs from five-year SJLIFE/CCSS European ancestry survivors (>95% BCCs occur in Non-Hispanic White survivors). An externally-validated general population keratinocyte cancer PRS from a large-scale analysis (N>300,000) was assessed in SJLIFE/CCSS using adjusted hazard ratios (HRs) from Cox proportional hazards regression, and cross-validated prediction performance metrics relative to a novel clinical risk prediction model in development in CCSS. Case-control frequencies were compared (SJLIFE; CCSS, diagnosed 1987-1999) for carrying rare P/LP variants in 19 syndrome-related genes tested on three major BCC gene panels (Blueprint, GeneDx, Invitae).

Results: Among the 9,429 survivors with WGS/array-based genotypes (51% female; median age=38y [IQR: 30-45y]; 782 BCCs), the keratinocyte cancer PRS showed a dose-response relationship with BCC risk, adjusting for maximum cumulative RT dose (top vs. bottom quintile HRs, combined: 2.8, 95% CI: 2.2-3.6, $P=2.0x10^{-16}$; SJLIFE: 4.2, 95% CI: 2.6-6.9; CCSS: 2.7, 95% CI: 2.0-3.6). Prediction performance after adding this PRS (AUC: 0.74, 95% CI: 0.69-0.77) to a newly-developed BCC clinical risk prediction model (AUC: 0.71, 95% CI: 0.67-0.75) was significantly improved (P=0.040). Among the 5,219 survivors with WES data (265 BCCs), 145 P/LP variants were detected in 18 BCC panel genes. Overall, the prevalence of carrying such P/LP variants was 3% (95% CI: 3-4%), but did not differ by BCC status.

Conclusion: Inherited genetic predisposition can inform subsequent BCC risk prediction, e.g., a keratinocyte cancer PRS exhibiting a strong dose-response relationship with BCC risk. Evaluating BCC gene panel P/LP variants showed limited utility among these high-risk survivors.