

Title: TRANSCRIPTOME-WIDE ASSOCIATION STUDIES UNCOVER GENETICALLY REGULATED EXPRESSION AND GENE-TREATMENT INTERACTIONS UNDERLYING SUBSEQUENT NEOPLASM RISK IN SURVIVORS OF CHILDHOOD CANCER

Authors: Michael J. Betti¹, Chang Li¹, Kendrick Li¹, Kerry Ye¹, Yan Chen¹, Jennifer N French¹, Kateryna Petrykey¹, Kevin Krull², Stephanie B. Dixon^{1,9}, Bonnie Ky³, Matthew J. Ehrhardt^{1,9}, Heather M. Conklin², Lisa M. Jacola², Angela Delaney^{1,4}, M. Monica Gramatges⁵, Chaya S. Moskowitz⁶, Eric J. Chow⁷, Kevin Oeffinger⁸, Joseph P. Neglia⁹, Lucie M. Turcotte⁹, Samuel W. Brady¹⁰, Kirsten K. Ness¹, Melissa M. Hudson^{1,11}, Gregory T. Armstrong¹, Yutaka Yasui¹, Yadav Sapkota¹

¹Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA

²Department of Psychology and Behavioral Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

³Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁴Department of Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, TN, USA

⁵Department of Pediatrics, Division of Hematology-Oncology, Baylor College of Medicine, Houston, TX, USA

⁶Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁷Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, WA, USA

⁸Department of Medicine, Duke University School of Medicine, Durham, NC, USA

⁹Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, USA

¹⁰Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

¹¹Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

Abstract

Background and aims: Subsequent neoplasms (SNs) are among the most common treatment-related adverse effects among survivors of childhood cancer. Prior genome-wide association studies have identified genetic variants associated with risk for individual SNs in survivors. However, no study to date has utilized a transcriptome-wide association studies (TWAS) approach to evaluate genetically regulated expression. We aimed to identify key transcripts influencing SN risk.

Methods: Across a multi-ancestry cohort of 4,279 survivors in the St. Jude Lifetime Cohort Study (SJLIFE), we imputed tissue-specific genetically regulated enhancer RNA (eRNA) and gene expression and performed Cox-based TWAS of three subsequent cancer incidence rates: all SNs, subsequent malignant neoplasms [SMNs], and SMNs excluding non-melanoma skin

cancers. Statistically significant associations were tested for replication in the Childhood Cancer Survivor Study (CCSS) cohort, and tumor-sample differential expression analysis identified associations with functional support in survivors for whom SN tumor tissue was available. Finally, interaction analysis was performed to identify TWAS associations modified by cancer therapy exposures.

Results: TWAS revealed seven eRNAs (four replicated) and 15 genes (three replicated) with at least suggestive association ($FDR < 0.1$) with a subsequent cancer phenotype, including two eRNAs and eight genes that showed altered expression in brain SNs compared with histologically normal tissue from the general population. Among these functionally supported associations were replicated eRNAs ENSR00000256952 and ENSR00000020877 and replicated genes *ANO8* and *GGCT*. Treatment exposures modified five TWAS associations. Among these were *AL079343.1* (breast), whose effect was modified by epipodophyllotoxins (interaction HR [95% CI]=0.79 [0.62–0.99] per 1 g/m², $p=0.04$) and chest radiation (interaction HR [95% CI]=1.96 [1.31–2.94] per 10 Gy, $p=1 \times 10^{-3}$), and *JUP* (brain), which was modified by abdominal radiation (interaction HR [95% CI]=7.80 [1.69–35.97] per 10 Gy, $p=8.42 \times 10^{-3}$).

Conclusions: These findings provide insights into the mechanisms of SN risk among childhood cancer survivors and identify gene-treatment interactions that may inform future risk stratification and treatment selection.

Abstract topic: AS05.s – Survivorship/late toxicity

Title length: 19/25 words

Abstract length: 291/300 words

