The genomic landscape of subsequent breast, meningioma, and thyroid neoplasms after treatment for childhood cancer: A report from the Childhood Cancer Survivor Study

Samuel W. Brady[1,2], Michael A. Arnold[3], Mingjuan Wang[4], Ramzi Alsallaq[2], Li Dong[2], Mohammad Aslam Khan[1], Wentao Yang[2], Kayla L. Stratton[5], Wei Liu[4], Yan Chen[6], Emily Plyler[2], Jacob Steele[2], Brent B. Powers[2], David Rosenfeld[2], Michael Edmonson[2], Sasi Arunachalam[2], Heather L. Mulder[2], Deokumar Srivastava[4], Michael Rusch[2], Vikki Nolan[6], Aaron McDonald[6], Lucie M. Turcotte[7], Cindy Im[7], John Easton[2], Zhaoming Wang[2,6], Wendy M. Leisenring[5], Miriam Conces[8], Joseph P. Neglia[7], Yutaka Yasui[6], Smita Bhatia[9], Jinghui Zhang[2*] and Gregory T. Armstrong[6*]

Abstract: While >85% of children with cancer will become five-year survivors, they are at substantially increased risk of developing subsequent neoplasms (SNs) in part due to DNA-damaging therapy. However, the effects of primary cancer therapy on the SN genomic landscape are unknown. We utilized biospecimens collected through the Childhood Cancer Survivor Study (CCSS) and employed whole-genome, exome, and RNA sequencing to analyze 199 SNs (median diagnosis age of 37.8 years, range 13.0-54.4) and matched germline tissue from 159 childhood cancer survivors, including 62 breast, 57 meningioma, and 42 thyroid SN patients. Overall, each SN type had similar somatic driver alterations to corresponding *de novo* cancers though at different frequencies, including increased frequency of kinase fusions and copy number alterations in thyroid SNs compared to *de novo* thyroid cancers. Meningioma and thyroid SNs had significantly elevated somatic single-nucleotide variant (SNV) and insertion-deletion (indel) burdens compared to *de novo* tumors from published cohorts such as The Cancer Genome Atlas, while breast SNs and *de novo* breast cancers had similar SNV and indel burdens. Prior treatment with nitrogen mustards, such as cyclophosphamide, was associated with increased levels of ubiquitous clock-like SNV mutational signature SBS5 in breast and meningioma SNs. We confirmed this association experimentally by treating cultured breast epithelial cells with an active cyclophosphamide metabolite followed by WGS, which revealed an SBS5-like signature induced by the treatment. In addition, we observed platinum-induced signatures SBS31 and SBS35 in 4 of 5 meningioma and thyroid SNs previously treated with platinum therapy, and identified and functionally validated *NF2* splice variants which were predicted to be platinum-induced in meningioma based on their occurrence at platinum signature hotspots. Driver alterations occurred evolutionarily early in most breast and thyroid SNs (12 of 14 multi-sample patients) as evidenced by their truncal status (detected in all samples at clonal variant allele fractions), while most meningioma patients (3 of 5) show intrapatient driver divergence, including a lack of shared mutations indicative of genetically independent tumors. Together, these results demonstrate the long-term impact of childhood cancer treatment on the genomes of SNs developing in adulthood, which may guide efforts to treat and prevent SNs.

Affiliations

[1]Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis TN, USA
[2]Department of Computational Biology, St. Jude Children's Research Hospital, Memphis TN, USA
[3]Department of Pathology, University of Colorado, Anschutz Medical Campus; and Department of Pathology and Laboratory Medicine, Children's Hospital Colorado, Aurora CO, USA
[4]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis TN, USA
[5]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle WA, USA
[6]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis TN, USA
[7]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
[8]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, OH, USA
[9]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA

*J.Z. and G.T.A. contributed equally and jointly supervised this work