

Telomere length-associated genetic variants and the risk of thyroid cancer after childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS)

Philip J. Lupo¹, Lindsay M. Morton², Yutaka Yasui³, Wendy M. Leisenring⁴, Gregory T. Armstrong³, Leslie L. Robison³, Smita Bhatia⁵, Maria M. Gramatges¹

¹Baylor College of Medicine, Houston, TX; ²National Cancer Institute, Bethesda, MD; ³St. Jude Children's Research Hospital, Memphis, TN; ⁴Fred Hutchinson Cancer Research Center, Seattle, WA; ⁵University of Alabama at Birmingham, Birmingham, AL

Character count: 2,548 (maximum 2,600)

Purpose: We previously reported an association between reduced telomere content and increased risk for radiation-related thyroid subsequent neoplasms (SNs) in childhood cancer survivors. We now extend this work to investigate associations between single nucleotide polymorphisms (SNPs) in the National Human Genome Research Institute-European Bioinformatics Institute (NHGRI-EBI) GWAS Catalog identified to influence telomere length and thyroid SN in a cohort of childhood cancer survivors.

Methods: The population included 5,324 5-year survivors of childhood cancer survivors participating in the CCSS with genome-wide SNP data generated using the Illumina HumanOmni5Exome array, who (1) developed thyroid SN (n=117) or (2) did not develop thyroid SN (n=5,207), censored by date of any SN, death, or last follow-up. Ancestry was estimated using HapMap data as the fixed reference population. Imputation was performed based on the 1000 Genomes Project reference haplotypes. For the analysis, we focused on SNPs in the NHGRI-EBI GWAS Catalog previously identified to influence telomere length (statistical significance threshold $P < 1.0 \times 10^{-5}$). Assuming an additive genetic model, we used multivariable Cox proportional hazards models to estimate the hazard ratio (HR), 95% confidence interval (CI), and P value for the association between each SNP and thyroid SN risk. Covariates evaluated included sex, primary cancer diagnosis, radiation exposure, and exposure to alkylating agents. Analyses were restricted to those of European ancestry to limit bias due to population stratification. Results were also stratified on radiation exposure and primary diagnosis, and the false discovery rate (FDR) was used to account for multiple comparisons.

Results: We identified 30 SNPs in the NHGRI-EBI GWAS Catalog associated with telomere length. Based on the sample size and the number of SNPs evaluated, we had 80% power to identify HRs between 1.7 and 2.0, based on minor allele frequencies (MAFs) of 10-40%. In multivariable analyses, when evaluating associations among those exposed to radiation to the neck, the top hit was rs621559 (HR=1.94, 95% CI: 1.16-3.24, $P=0.01$), an intronic SNP in *WDR65*. However, after applying the FDR at <0.05 , no SNPs were associated with thyroid SN risk overall, nor after stratifying on radiation exposure or primary diagnosis.

Conclusions: There is an inverse relationship between telomere content and thyroid SN among childhood cancer survivors. Our study was unable to identify an association between common SNPs influencing telomere length and thyroid SN. The observed relationship between reduced telomere content and thyroid SN could possibly be due to alternative molecular mechanisms such as rare or novel variants, or defects in specific genes related to telomere maintenance.