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Polygenic Risk of Subsequent Thyroid Cancer after Childhood Cancer: A report from St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS)

Background:
Subsequent thyroid cancer (STC) is among the most common malignancies in childhood cancer survivors, especially those with thyroid exposure to radiotherapy (RT). Identification of genetic risk factors may inform screening practices.

Methods:
Twelve SNPs were previously identified as thyroid cancer risk loci in the general population of European ancestry. A polygenic risk score (PRS) was calculated as a sum of risk alleles carried by a survivor, weighted by the natural logarithm of the published per-allele odds ratios (range: 1.2-1.8). With piecewise exponential models, associations of STC rates with PRS were assessed, both overall and stratified by neck RT exposure. Models were adjusted for sex, age at primary diagnosis, attained age, neck RT dose, epipodophyllotoxin therapy, and eigenvectors within survivors of European ancestry from SJLIFE with whole-genome sequencing data and CCSS with SNP data imputed to Haplotype Reference Consortium.

Results:
Among 2,324 SJLIFE survivors, 61 (43 with, 18 without neck RT) developed STC. The rate of STC was increased by 5.3-fold (95% confidence interval (CI), 2.2-12.6) and 3.1-fold (CI, 1.3-7.7) for surviors in the third and second PRS tertiles, respectively, compared to those in the first tertile, with corresponding cumulative incidence at age of 40 years of 5.3% (CI, 3.3-7.3%), 2.5% (CI, 1.1-3.9%), and 1.0% (CI, 0.005-2.0%), respectively. Stratified by neck RT, the corresponding rate increases were 7.6 (CI, 2.3-25.3) and 3.8 (CI, 1.1-13.4), respectively, among surviors exposed to neck RT; however, no association was observed among survivors without neck RT (only 18 STC cases). Replication was performed among 4,302 CCSS survivors, 100 (61 with, 39 without neck RT) developed STC. The rates of STC were increased by 2.3-fold (CI, 1.4-3.9) and 1.7-fold (CI, 1.0-2.9) for surviors in the third and the second PRS tertiles, compared to those in the first tertile. The similar significant associations were observed in surviors with and without neck RT (P_{trend} = 0.04 and 0.02, respectively).

Conclusions:
High PRS conferring STC risk can inform screening practices and help personalize and improve survivorship care.