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Topic category: Pediatric cancer

Subsequent neoplasm risk associated with rare variants in DNA repair and clinical radiation sensitivity syndrome genes: A report from the Childhood Cancer Survivor Study

Background: Radiotherapy for childhood cancer is associated with strikingly elevated risk for developing subsequent neoplasms (SNs). Whether mutations in DNA repair and radiation sensitivity genes modulate SN risks is largely unknown.

Methods: We conducted whole-exome sequencing in 5105 long-term childhood cancer survivors of European descent (mean follow-up=32.7 years). SnpEff and ClinVar identified potentially damaging rare variants in 476 DNA repair or radiation sensitivity genes. Conditional logistic regression assessed SN risk associated with these variants aggregated by gene or pathway (N=155 with ≥5 carriers). Controls were matched on sex, childhood cancer type and diagnosis age, radiation dose to the SN site, and survival. Exact p-values were calculated by permutation. Analyses used all survivors or subsets stratified on radiation dose.

Results: A total of 1108 (21.7%) survivors developed at least one SN type known to be related to ionizing radiation exposure (e.g., breast cancer, basal cell carcinoma, meningioma, thyroid cancer, sarcoma). Radiation-related SN risk was associated with homologous recombination (HR) gene variants for SN sites that received >0-<10 Gy (20.9% cases, 11.0% controls; odds ratio [OR]=2.20, 95% confidence interval [CI] 1.52-3.18; $P=1.41x10^{-4}$), most notably for *FANCM* (3.1% cases, 0.5% controls; OR=9.91, 95%CI 3.73-26.4; $P=2.85x10^{-4}$). For radiation-related SNs at sites with higher doses (≥10 Gy), associations were not observed for the HR pathway (14.4% cases, 12.4% controls, P=0.17) but were observed for two individual genes implicated in double-strand DNA break repair, *EXO1* (1.8% cases, 0.4% controls; OR=6.50, 95%CI 3.49-12.1; $P=7.43x10^{-4}$) and *NEIL3* (0% cases, 1.0% controls; $P=3.23x10^{-4}$).

Conclusions: In this discovery study, we identified dose-specific novel associations between SN risk after radiotherapy for childhood cancer and potentially damaging rare variants in genes involved in double-strand DNA break repair, particularly HR. If replicated, these results could impact long-term screening of childhood cancer survivors and risk-benefit assessments of treatment approaches.