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Title: Genome-wide association study of meningioma as a subsequent neoplasm: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE)

Survivors of childhood cancer treated with cranial irradiation have a dose-dependent increased risk of meningiomas, which may cause significant morbidity. However, surveillance guidelines are not well established. To identify a high-risk population who may benefit from meningioma surveillance, we conducted a genome-wide association study to identify genetic variants predisposing certain childhood cancer survivors to radiation-associated meningioma. The study pooled data from individuals of European descent from CCSS and SJLIFE, including 167 survivors who developed meningioma (median age at meningioma diagnosis=30.0 years; 84% had ≥ 10 Gy cranial irradiation) and 5732 survivors who did not develop a subsequent neoplasm during follow-up (median age at last follow-up=33.6 years; 48% had ≥ 10 Gy cranial irradiation). After genotyping and imputation, data were available for 16,958,466 single nucleotide polymorphisms (SNPs) that passed quality control thresholds. We used Cox proportional hazards models with age as the time scale, adjusted for cohort, cranial irradiation ≥ 10 vs. < 10 Gy, receipt of alkylating agent- or platinum-containing chemotherapy, and population eigenvectors to identify associated SNPs. The strongest association was observed for a locus at 7q31.1 marked by rs140784593 (minor allele frequency=0.01 in controls, 0.04 in cases; per-allele hazard ratio=7.13, 95% confidence interval=3.97-12.81; permutation-based $P=1.00 \times 10^{-8}$). Results were consistent in both cohorts and also when the pooled population was restricted to children with first primary acute lymphoblastic leukemia or first primary central nervous system tumors. The intergenic SNP rs140784593 maps near *GPR85*, an evolutionarily-conserved G-protein-coupled receptor involved in intracellular signaling that is highly expressed in the brain. Childhood cancer survivors with inherited predisposition to radiation-associated meningioma may represent a subgroup of

individuals who could benefit from more intensive surveillance (e.g., routine magnetic resonance imaging) during long-term follow-up.