Richard MA[1], Mostoufi-Moab S[2], Rathore N[1], Brown AL[1], Chanock SJ[3], Friedman DN[4], Gramatges MM[1], Howell RM[5], Kamdar KY[1], Leisenring W[6], Meacham LR[7], Morton LM[3], Oeffinger K[8], Robison LL[9], Sapkota Y[9], Sklar C[4], Yasui Y[9], Armstrong GT[9, 10], Bhatia S[11], Lupo PJ[1].

1 Section of Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, TX;

2 Division of Endocrinology and Division of Oncology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA;

3 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD;

4 Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY;

5 Division of Radiation Oncology, Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX;

6 Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA;

7 Division of Hematology/Oncology/BMT, Department of Pediatrics, Emory University, Atlanta, GA;

8 Department of Medicine, Duke University and Duke Cancer Institute, Durham, NC;

9 Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN;

10 Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN;

11 Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL.

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Genetic and treatment risks for diabetes mellitus (DM) in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime (SJLIFE) cohorts

Background: Childhood cancer survivors face increased risk for DM, a polygenic trait also attributable to cancer treatment exposures, particularly abdominal radiation. We aimed to characterize the role of genetic and treatment risk factors for DM among two large cohorts of childhood cancer survivors.

Methods: We performed a nested case-control genome-wide association study for DM managed with oral medications in the original CCSS cohort (diagnosed 1970-1986). Logistic regression was conducted in the total sample (N = 5083) and stratified by 1) European ancestry (EA) and 2) abdominal radiation. Replication of suggestive variants ($P<1\times10^{-7}$) using Fisher's exact test was performed in independent cohorts: i) CCSS expansion diagnosed 1987-1999 (N = 2588) and ii) SJLIFE diagnosed 1962-2012 (N = 2182). To evaluate the effect of cancer treatment on the background genetic predisposition to DM, we estimated standardized effect sizes (Z') among EA survivors in each abdominal radiation group for 398 index variants from the largest population-based EA DM study. Radiation group Z' estimates were compared using linear regression.

Results: In the original CCSS cohort we identified nine variants associated with DM and provide further support for four linked variants in the *ERCC6L2* locus. Among all survivors, the rs55849673-A allele was associated with increased odds for DM among survivors in the original CCSS cohort (minor allele frequency [MAF]-cases = 0.055; MAF-controls = 0.024; adjusted odds ratio [aOR] = 2.9, 95% CI: 2.0-4.2, $P = 3.7\times10^{-8}$). Allele frequencies were consistent in the CCSS expansion (MAF-cases = 0.075; MAF-controls = 0.028; P = 0.07) and SJLIFE (MAF-cases = 0.036; MAF-controls = 0.027; P = 0.5). Additionally, rs55849673-A estimates were consistent among EA survivors and stronger among survivors not treated with abdominal radiation (MAF-cases = 0.052; MAF-controls = 0.021; aOR = 3.6, $P = 1.6\times10^{-6}$). Notably, in the CCSS expansion all rs55849673-A EA carriers who developed DM did not receive abdominal radiation (MAF-cases = 0.1; MAF-controls = 0.026; P = 0.04). More broadly, the Z' of population-based DM index variants were 78% lower in survivors treated with abdominal radiation than survivors not treated with abdominal radiation (beta = 0.22; P = 0.01), indicating the background genetic risk for DM may be altered by treatment.

Conclusions: We provide evidence for a novel locus of DM in childhood cancer survivors. This locus is a regulatory region associated with expression of *ERCC6L2*, a gene implicated in an East Asian population-based DM study. Taken together, our findings support the overwhelming effect of abdominal radiation on DM risk in childhood cancer survivors, relative to other risk factors, and provide insight on a genetic locus that may be useful for DM risk prediction in the context of cancer treatment.