

Title: Genetic study of diabetes mellitus risk in diverse populations of survivors of childhood cancer: a report from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS)

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Background: Diabetes mellitus (DM) is an established late effect of cancer treatment among long-term survivors of childhood cancer. Genetic factors underpinning DM in diverse populations of survivors have not been well studied.

Methods: We conducted a multi-ancestry genome-wide association study (GWAS) for clinically ascertained DM among survivors of European (EUR; N=3,102 with 261 cases) and African (AFR; N= 574 with 43 cases) ancestry from SJLIFE. Replication analyses were performed between ancestries in SJLIFE and in EUR survivors in CCSS (N=5,965; 270 self-reported cases). Two published type 2 diabetes (T2D) polygenic risk scores (PRSs) were assessed in survivors: a 338-variant multi-ancestry PRS (N~1.4 million; 49% non-EUR descent) and a ~6.9 million-variant EUR-only PRS (N~160K; DIAGRAM Consortium and UK Biobank Study). Treatment-related DM risk effect modification was evaluated for abdominal irradiation and alkylating agents.

Results: In SJLIFE AFR survivors, one novel locus with suggestive significance was identified (5p15.2: OR=10.19, P=5.1x10⁻⁷), replicating in both SJLIFE EUR (P=0.011) and CCSS EUR survivors (P=0.021). A EUR-specific genome-wide significant association at 8q11.21 (*SNTG1* intronic variant; OR=1.99; P=4.4x10⁻⁸) was replicated in CCSS (P=8.1x10⁻³). Two other loci with suggestive associations (P<5x10⁻⁶) in SJLIFE EUR survivors replicated in SJLIFE AFR survivors (P<0.05), achieving genome-wide significance in multi-ancestry meta-analysis (2p25.3: OR=2.05, P=4.5x10⁻⁸; 19p12: OR=2.43 P=5.7x10⁻⁹). Each of the three novel trans-ancestral loci overlapped putative Polycomb-repressed regions, i.e., chromatin-based gene regulation elements, in pancreatic cells and displayed treatment-related effect heterogeneity across ancestry groups. Notably, AFR survivors with risk alleles experienced disproportionately greater DM risk if treated with alkylating agents (2p25.3: OR=3.95; 19p12: OR=5.74; 5p15.2: OR=17.81). Increases in the DM odds per multi-ancestry PRS standard deviation were consistent in survivors across ancestries (SJLIFE EUR: OR=1.84, P=1.1x10⁻¹⁶; SJLIFE AFR: OR=1.80, P=2.8x10⁻³, CCSS EUR: OR=1.60, P=8.4x10⁻¹³). However, DM risk association with the EUR-only PRS was absent in AFR survivors (OR=0.97, P=0.95).

Conclusions: Multi-ancestry genetic analyses revealed four novel DM risk alleles, including three trans-ancestral loci associated with disproportionately greater alkylating agent-related risk among African-ancestry survivors. Furthermore, an external multi-ancestry T2D PRS was associated with increased risk

in diverse ancestry survivors, whereas a EUR-only PRS was not useful for African-ancestry survivors. This study supports precision diabetes surveillance and survivorship care for all childhood cancer survivors, including those in minority ancestry groups.