

Title: DNA METHYLATION AND OBESITY IN SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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Purpose: Epigenetic mechanisms are important regulators of body mass index (BMI) in the general population but have not been explored among survivors of pediatric cancer. Because ALL treatment places individuals at high risk for adverse metabolic outcomes, we evaluated the association between DNA methylation and obesity among adult survivors of childhood ALL.

Methods: We selected 96 survivors of ALL based on the CCSS 2007 Follow-Up using "extreme phenotype" sampling: 48 obese (BMI \geq 30.0 kg/m²) and 48 normal weight (BMI=18.5-24.9 kg/m²). Subjects were frequency-matched on age at diagnosis, gender, length of follow-up, cranial radiotherapy (CRT, yes/no), and genetic ancestry. The Illumina HumanMethylation450 BeadChip was used to determine DNA methylation in buccal cells collected at baseline. Using linear regression, we compared DNA methylation beta values between obese and normal-weight survivors at 39 BMI-associated loci identified in epigenome-wide association studies (EWAS) of BMI in the general population. False discovery rate (FDR) was used to correct for multiple testing.

Results: Overall, the mean ages at diagnosis, baseline, and follow-up were 6, 21, and 34 years, respectively. Among the 39 previously identified BMI-DNA methylation loci, 37 passed quality control measures. A locus in *ABCG1* (cg06500161) was associated with obesity in ALL survivors ($\beta_{\text{obese}}=0.64$ vs. $\beta_{\text{normal-weight}}=0.61$, $p=0.0001$, $\text{FDR}=0.005$). Effect estimates did not differ by CRT status. Five additional loci were nominally significant ($p<0.05$) with similar effect estimates as previous EWAS, including cg26403843 (*RNF145*, $\beta_{\text{obese}}=0.41$ vs. $\beta_{\text{normal-weight}}=0.37$, $p=0.0034$, $\text{FDR}=0.064$).

Conclusions: A previously identified BMI-DNA methylation locus in *ABCG1* was associated with obesity among ALL survivors. *ABCG1* is involved in lipid homeostasis, and its promoter hypermethylation is strongly associated with risk of coronary heart disease. Further, cg06500161 is associated with insulin-related traits and lipid subfractions in the general population. Larger independent studies are needed to replicate these findings and to identify novel BMI-DNA methylation loci among childhood ALL survivors.

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