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Epigenetic mechanisms underlying disparities in endometrial cancer (EC) outcomes: race-specific patterns of DNA methylation associated with molecular subtypes and EC survival

Endometrial cancer (EC) is the 4th most common cancer in US women, with striking disparities in race-specific outcomes where Black patients have a significant higher incidence of mortality. The factors that contribute to these differences are complex, and likely include racial differences in epigenetic landscapes. To investigate race-specific epigenetic differences in EC tumor characteristics and outcome, we utilized the most recent EC data within the Cancer Genome Atlas (TCGA). Genome-wide CpG methylation data for more than 850k CpG sites were analyzed across a total of 233 tumor samples collected from n=52 Black patients and n=181 White patients. Race-independent and race-specific associations between CpG methylation and molecular subtypes were examined using linear regression with empirical bayes moderation. Race-independent and race-specific associations between CpG methylation and progression-free survival (PFS) were also examined using Cox proportional-hazards regression. After Bonferroni correction, 106,033 CpGs displayed race-independent association with molecular subtypes. The highest significance in relation to molecular subtypes was observed for DNA methylation within the mismatch repair gene mutL homolog 1 (*MLH1)*, a known prognostic marker of EC. Race-specific analysis identified CpG methylation association with molecular subtypes for 13 genes identified in tumors from Black patients specifically. Race-specific survival-associated CpGs were also identified where 1,940 CpG sites representing 1,119 unique genes were identified in tumors from White patients while zero were identified in tumors from Black subjects. Identification into the racial differences in EC epigenetics could provide insight into strategies to improve outcomes and reduce the disparities.