Methylomic basis of survival disparities among Black and White women with high-grade serous ovarian cancer

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Ovarian cancer is the most lethal gynecologic malignancy in the U.S., and Black women with ovarian cancer have worse survival compared to White women. The causes of these disparities remain elusive as prior research suggests that it is not entirely due to differential access to care, tumor characteristics, or receipt of guideline-adherent treatment. Moreover, most research on ovarian cancer is from White women, which has hindered the discovery of novel factors important for prognosis in underrepresented minority groups.

DNA methylation, the presence of a methyl group on a cytosine followed by a guanine nucleotide, provides a unique opportunity to investigate disparities as differences in lifestyle and sociocultural conditions across racial and ethnic groups may manifest as alterations in tumor DNA methylation, resulting in phenotypic differences between populations. In ovarian cancer, previous methylation profiling studies of White women identified DNA methylation signatures associated with survival and biomarkers that could be informative for the development of targeted therapies, yet, the relevance of these findings among Black women is unknown.

In the present study, we will leverage epidemiologic, molecular, and outcome data from three well-established observational studies to compare genome-wide profiles of tumor DNA methylation from Black and White women with ovarian cancer in association with prognosis. We will focus our efforts on the most common and one of the deadliest subtypes of ovarian cancer, high-grade serous ovarian cancer (HGSOC). Our prior work shows that Black women with ovarian cancer have distinct genetic and molecular features compared to White women and thus, we hypothesize that Black women will have distinct tumor DNA methylation signatures associated with inferior survival compared to White women. Using DNA methylation data measured on the Illumina MethylationEPIC array, data dimension reduction methods will be used to determine HGSOC DNA methylation signatures that are associated with survival. We will conduct these analyses among the overall study population as well as Black and White women separately to determine differentially methylated regions associated with outcomes that are specific to each race and those that are shared across racial groups. Next, we will investigate the association of pre-diagnostic exposures that have the potential to alter DNA methylation states (e.g., obesity) with outcome-associated DNA methylation signatures. The third aim will infer tumor cell composition from DNA methylation using a novel cell mixture deconvolution method and will examine whether cell composition is associated with risk of mortality. Comparing DNA methylation across populations has important applications as this work will advance the discovery of novel molecular targets among an underrepresented minority group, with the ultimate goal of reducing the survival gap between Black and White women with ovarian cancer.