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Racial disparities in molecular subtypes of endometrial cancer☆

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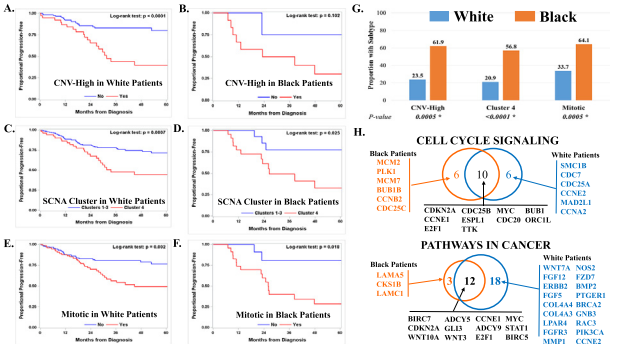
HIGHLIGHTS

- Aggressive molecular subtypes were more frequently in Black endometrial cancers.
- The mitotic subtype consistently indicated worse progression-free survival in Black patients.
- Race-associated and –independent up-regulation in cell cycle signaling and cancer pathways.
- Enrichment patterns in mitotic signaling may represent therapeutic opportunities.

GRAPHICAL ABSTRACT



Progression-free survival in White (**A, C, E**) or Black (**B, D, F**) endometrial cancer patients with versus without the copy number variant (CNV)-high subtype (**A, B**), the somatic copy number alterations (SCNA) cluster 4 subtype (**C, D**), or the transcript-based mitotic subtype (**E, F**). Survival distributions compared using log-rank testing. Bar chart displaying the proportion of patients with the more-aggressive copy number variant (CNV)-high subtype, the somatic copy number alterations (SCNA) cluster 4 subtype, or the transcript-based mitotic subtype (**G**). Fisher's exact testing was used to compare categorical variables. Venn diagram of the most significantly up-regulated transcripts in cell cycle signaling and in pathways in cancer in Black and/or in White endometrial cancer patients with mitotic versus non-mitotic subtypes with >2-fold change elevation and a false discovery rate < 0.01 (**H**).

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ABSTRACT

Objectives. Racial differences in the molecular subtypes of endometrial cancer and associations with progression-free survival (PFS) were evaluated.

Methods. Molecular, clinical and PFS data were acquired from the Cancer Genome Atlas (TCGA) including classification into the integrative, somatic copy number alteration and transcript-based subtypes. The prevalence and prognostic value of the aggressive molecular subtypes (copy number variant [CNV]-high, cluster 4 or mitotic) were evaluated in Black and White patients.

☆ An abstract and plenary presentation for this project were presented at the Society for Gynecologic Oncology 2017 Annual Meeting for Women's Cancer. This work was presented as a poster at the Military Health System Research Symposium on August 29, 2017.

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Results. There were 337 patients including 14% self-designated as Black, 27% with advanced stage, and 82% with endometrioid histology. The CNV-high subtype was more common in Black than White patients (61.9% vs. 23.5%, $P = 0.0005$) and suggested worse PFS in Black patients (hazard ratio [HR] = 3.4, $P = 0.189$). The cluster 4 subtype was more prevalent in Black patients (56.8% vs. 20.9%, $P < 0.0001$) and associated with worse PFS in Black patients (HR = 3.4, $P = 0.049$). The mitotic subtype was more abundant in Black patients (64.1% vs. 33.7%, $P = 0.002$), indicated worse PFS in Black patients (HR = 4.1, $P = 0.044$) including the endometrioid histology (HR = 6.1, $P = 0.024$) and exhibited race-associated enrichment in cell cycle signaling and pathways in cancer including *PLK1* and *BIRC7*. All of these aggressive molecular subtypes also indicated worse PFS in White patients, with unique enrichments in mitotic signaling different from Black patients.

Conclusions. The aggressive molecular subtypes from TCGA were more common in Black endometrial cancer patients and indicated worse PFS in both Black and White patients. The mitotic subtypes also indicated worse PFS in Black patients with endometrioid histology. Enrichment patterns in mitotic signaling may represent therapeutic opportunities.

1. Introduction

Endometrial cancer is the second most prevalent cancer in women in the United States [1]. Though the incidence of endometrial cancer is roughly equal for Black and White women, Black women are more likely to be diagnosed at advanced stages with high-risk histology and higher-grade disease [2,3]. The number of deaths reported from 2009 to 2013 per 100,000 persons was 7.9 for Black women compared to 4.1 for White women [4], highlighting the differences in survival between racial groups. Racial disparities are undoubtedly multifactorial and due in part to differences in socioeconomic factors, access to care, and comorbidities [5,6]. However, more recent investigations suggest disparities in outcome continue to persist despite evidence of equal care [7–10]. Analysis by the United States Census Bureau project an increased incidence in endometrial cancer, particularly in the aggressive histologic subtypes, which disproportionately affect Black women [11]. Pursuit of modifiable and targetable elements of endometrial cancer are essential for this vulnerable group.

Various levels of molecular characterization of cancers including endometrial cancer are being pursued with the goal of improving early detection, stratifying risk, personalizing treatment and preventing cancer. The Cancer Genome Atlas (TCGA) research network conducted exomic, whole genome and RNA sequencing with assessments of microsatellite instability (MSI) status, copy number variant (CNV) calls, and/or somatic copy number alterations (SCNA), and defined three distinct molecular subtypes of endometrial cancer with enhanced prognostic value over histologic subtype and grade [12]. The first set of molecular subtypes are the integrative molecular subtypes, including the ultra-mutated DNA polymerase epsilon (POLE), hyper-mutated MSI, CNV-low and CNV-high subtypes. The second set of molecular subtypes categorize cases as SCNA clusters 1–4. The third set of molecular subtypes are based on unsupervised k-means clustering of RNA sequencing-based transcript expression patterns classified as the hormonal, immunoreactive and mitotic subtypes. TCGA then demonstrated that the transcript-based molecular subtypes were significantly correlated with the four integrative subtypes ($P < 0.0001$), and used supervised analyses of RNA sequencing, reverse phase protein array and DNA methylation data to show that the hypermuted *POLE* subtype was associated with a cellular metabolism gene signature and high protein expression of ASNS and CCNB1 whereas the MSI subtype was associated with reduced *MLH1* mRNA expression, low protein expression of PTEN, high levels of phospho-AKT and promoter hypermethylation of *MLH1* [12]. In addition, the CNV-low subtype was associated with elevated mRNA expression of progesterone receptor (*PGR*) and elevated protein levels of RAD50 [12]. In contrast, the CNV-high subtype was associated with dysregulation of cell cycle genes including *CCNE1*, *PIK3CA*, *MYC* and *CDKN2A*, and with proteins including elevated expression of TP53 consistent with the frequent mutations observed in *TP53* in this group and with reduced levels of phospho-AKT [12].

Uterine serous cancers are an aggressive histology associated with poor outcome whereas most endometrioid cancers are associated with a favorable prognosis. The aggressive CNV high, SCNA cluster 4 and mitotic subtypes may help distinguish morphologically indistinguishable endometrioid tumors with poor prognosis that require more aggressive treatment. As an extension of our prior studies of racial disparities in endometrial cancer, this study sought to determine whether the molecular subtypes of endometrial cancer varied by self-designated race. We further evaluated the prognostic value of these molecular subtypes overall and separately in White and Black patients with endometrial cancer and within the endometrioid histology. Additionally, we explored potential therapeutic targets in Black and White patients with the aggressive subtypes.

2. Methods

This research investigation utilized public data from the Cancer Genome Atlas (TCGA). An institutional review board (IRB) waiver was obtained from Western IRB in accordance with use of publicly available de-identified data (14-1679). TCGA Uterine Corpus Endometrial Carcinoma (UCEC) provisional clinical data and molecular subtype annotation [12] were extracted from *cgdsr* (version 1.2.5) package in R (version 3.1.2) in August 2016. Statistical analyses were conducted with Statistical Analysis System (SAS) version 9.4 or using *R*. This study investigated disparities in molecular subtypes in self-described Black compared with White endometrial cancer patients. Patients designated to be another racial group or with unknown race information were excluded. Ethnicity data was missing in 50% of Black patients and 28% of the White patients, and was not taken into account in this investigation.

Fisher's exact test was used to compare differences for categorized variables. Three sets of molecular subtypes, including integrative subtypes, SCNA subtypes, and transcript-based subtypes as defined by TCGA were involved in this study, with the difference between Black and White patients either based on multi-category (original classification) or two-category (combined as the less aggressive subtypes vs. the more aggressive subtype) evaluated. Odds ratio and 95% confidence intervals (CI) were estimated from logistic regression modeling. The primary outcome was progression-free survival (PFS), which was calculated in months from diagnosis to disease progression or death due to cancer as defined by TCGA. Overall survival was not included in this study given the limited number of deaths in the TCGA UCEC cohort, especially for Black patients. The association between race (Black vs. White) or molecular subtypes (more aggressive vs. less aggressive) with PFS was evaluated using Cox proportional hazards model. Hazard ratio (HR) for risk of disease progression and 95% CI were estimated using Firth's penalized likelihood method. The impact of molecular subtype on PFS was examined in endometrial cancer patients, as well as in the subset with endometrioid-histology, with analyses conducted