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

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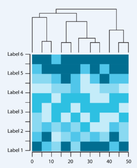
Background

- Endometrial cancer (EC), cancer of the uterine lining, is expected to have 66,200 new cases in 2023.
- The Cancer Genome Atlas (TCGA) is a publicly-available database of genomic and epigenomic cancer tumor data.
- Molecular Subtypes: defined by gene expression characteristics of tumors.
  - Copy-number High (CN high)/TP53mut
  - Microsatellite Instability (MSI) hypermutated
  - Copy-number Low (CN low)/TP53wt
  - *POLE* ultramutated
- CN high found to have highest risk of death and association with unfavorable clinicopathologic factors; *POLE* found to have the lowest risk of death.
- Disparities exist in race-specific outcomes, where Black patients have a higher incidence of mortality.
- We aimed to identify race-specific epigenetic differences that may contribute to this disparity.

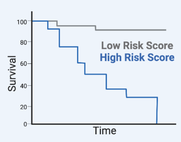
Research Workflow

Subset TCGA Uterine Corpus Endometrial Cancer data to patients with methylation and transcript data.

Race-independent and race-specific associations for CpG methylation and molecular subtypes using linear regression with empirical Bayes moderation.



Race-independent and race-specific associations for CpG methylation and progression-free survival (PFS) using Cox proportional-hazards regression.



Acknowledgement

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Results

Race, Histological Type, and Molecular Subtype

	Endometrioid					Serous				
Race	TP53mut/CNH (*N*%)	TP53wt/CNL (*N*%)	MSI (*N*%)	POLE (*N*%)	Total	TP53mut/CNH (*N*%)	TP53wt/CNL (*N*%)	MSI (*N*%)	POLE (*N*%)	Total
American Indian	0	0	1 (100.00)	0	1	0	0	0	0	0
Asian	0	3 (50.00)	2 (33.33)	1 (16.67)	6	2 (100.00)	0	0	0	2
Black	8 (15.38)	17 (32.69)	21 (40.38)	6 (11.54)	52	21 (87.50)	0	2 (8.33)	1 (4.17)	24
Hawaiian	2 (40.00)	1 (20.00)	1 (20.00)	1 (20.00)	5	1 (100.00)	0	0	0	1
White	21 (11.60)	74 (40.88)	71 (39.23)	15 (8.29)	181	49 (77.78)	10 (15.87)	4 (6.35)	0	63
Total	31 (12.65)	95 (38.78)	96 (39.18)	23 (9.39)	245	73 (81.11)	10 (11.11)	6 (6.67)	1 (1.11)	90

Table 1. Demographic breakdown of TCGA endometrial tumor sample data, stratified by tumor histology type, race, and molecular subtype.

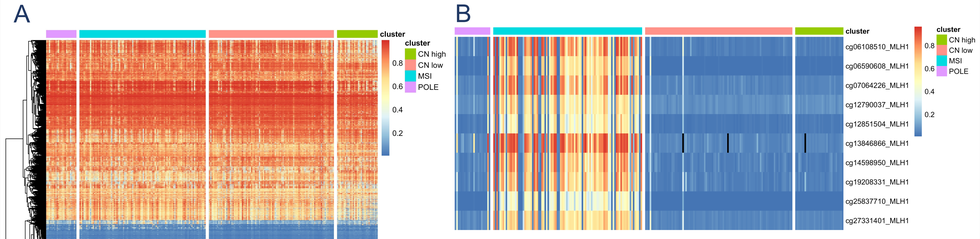

Figure 1. (A) Heat map depicting methylated CpG sites in endometrioid tumors associated with molecular subtypes CN high/TP53mut, CN low/TP53wt, MSI, and POLE, and (B) the ten CpG sites with the strongest methylation association—all found within the mutL homolog 1 (*MLH1*) gene.

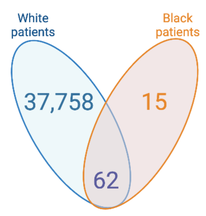

Figure 2. CpG sites significantly associated with subtype in endometrioid tumors, stratified by race.

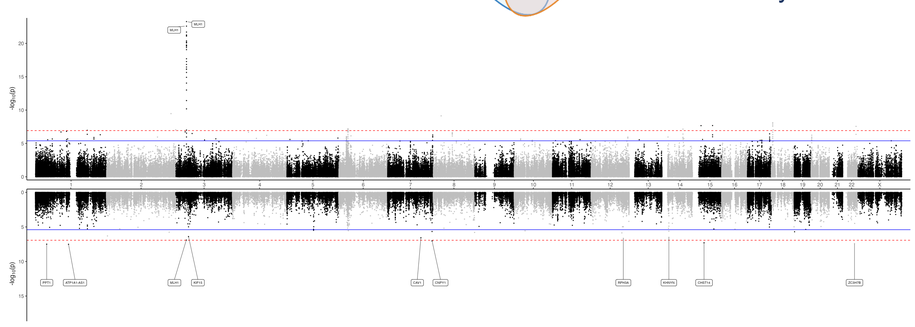

Figure 3. Miami plot depicting CpG sites in endometrioid tumors where methylation is either positively (upper plot) or negatively (lower plot) associated with molecular subtype, comparing MSI to POLE.

Results

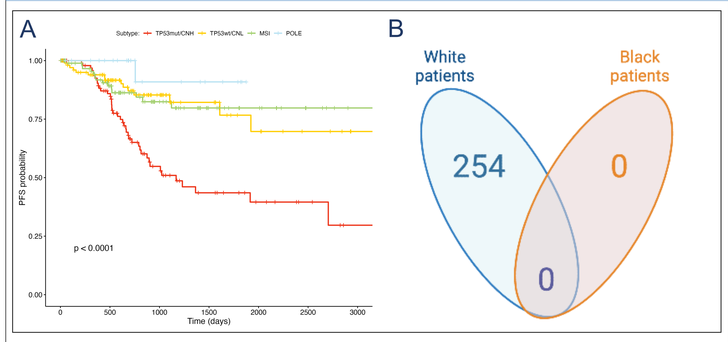

Figure 4. (A) Kaplan-Meier curve depicting PFS by molecular subtype for tumors for all 335 patients. (B) CpG sites significantly associated with survival in endometrioid tumors, stratified by race.

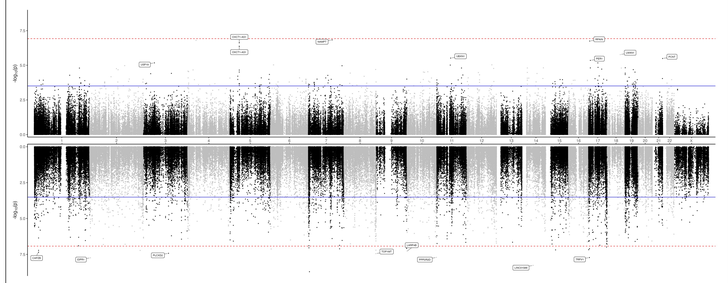

Figure 5. Miami plot depicting CpG sites in endometrioid tumors where methylation is associated with PFS, controlling for race.

Conclusions and Future Directions

- 61,128 CpGs displayed race-independent association (p<0.01) with molecular subtypes; CpGs with the most significant association were all found within the mutL homolog 1 (*MLH1),* which is a known prognostic marker of EC.
- Differentially methylated CpGs associated with molecular subtypes linked to three genes (*LINC02609*, *LY6E*, and *AP005205.3*) were identified in tumors from Black patients.
- Differentially methylated CpGs associated with survival were identified—254 CpG sites representing 165 unique genes in tumors from White patients while zero CpGs in tumors from Black subjects were significant.
- Next steps include investigation of transcriptomics for significant genes
- Understanding the racial differences in EC epigenetics could provide insight into strategies to improve outcomes and reduce the disparities.

Citations

1. Levine, D. A. (2013). Integrated genomic characterization of endometrial carcinoma. Nature, 497(7447), 67-73.
2. Doghri R, Houcine Y, Boujelbène N, et al. Mismatch Repair Deficiency in Endometrial Cancer: Immunohistochemistry Staining and Clinical Implications. *Appl Immunohistochem Mol Morphol*. 2019;27(9):678-682. doi:10.1097/PAI.0000000000000641
3. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*. 2023;73(1):17-48. doi:10.3322/caac.21763