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Disease progression, survival, and molecular disparities in Black and White patients with endometrioid endometrial carcinoma in real-world registries and GOG/NRG oncology randomized phase III clinical trials

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Abbreviations: U.S, United States; EEC, endometrioid endometrial carcinoma; SEER, Surveillance, Epidemiology, and End Results Program; NCDB, National Cancer Database; AACR, American Association of Cancer Research; GENIE, Genomics Evidence Neoplasia Information Exchange; RCTs, randomized phase III clinical trials; IRB, Institutional Review Board; FIGO, International Federation of Gynecology and Obstetrics; CRD, cancer related death; NCD, non-cancer death; PFS, progression free survival; OS, overall survival; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence intervals; PSM, propensity score matching; LVSI, lymphovascular space invasion; SMD, standardized mean difference.; TCGA, the Cancer Genome Atlas.

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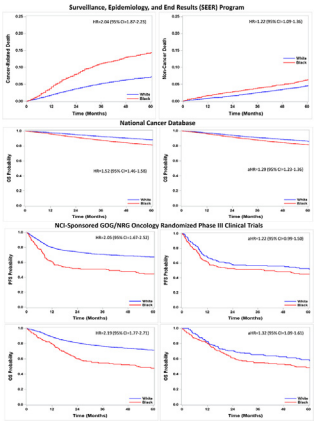
HIGHLIGHTS

- Risk of cancer-related and non-cancer-related death was 200% and 22% higher in Black vs. White patients with EEC in SEER.
- Risk of all-cause death was 1.52 (1.46–1.58) dropping to 1.29 (1.23–1.36) in matched NCDB Black vs. White patients.
- Black vs. White patients had fewer *PTEN*, *PIK3R1*, *FBXW7*, *NF1*, *mTOR* and *CCND1* mutations and similar TMB-high status.
- Advanced/recurrent disease, grade 3, and worse performance status were more common in Black vs. White EEC patients in RCTs.
- Risk of death in Black vs. White patients in RCTs was 2.19 (1.77–2.71), persisting in matched analysis [1.32 (1.09–1.61)].

GRAPHICAL ABSTRACT

Probability of cancer-related (row 1, left) and non-cancer death (row 1, right) in White or Black patients with endometrioid endometrial cancer (EEC) in SEER. Overall survival (OS) in Black vs. White patients with EEC in the original cohort (row 2, left) and propensity-score matched cohort (row 2, right) in the National Cancer Database. Progression-free survival (PFS, row 3) and overall survival (OS, row 4) in Black vs. White patients with EEC in the original cohort (left) or exactly matched and balanced cohort (right). Hazard ratio (HR) or adjusted HR (aHR) and 95% confidence interval (CI) were also included.



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ABSTRACT

Objective. Investigate racial disparities in outcomes and molecular features in Black and White patients with endometrioid endometrial carcinoma (EEC).

Methods. Black and White patients diagnosed with EEC who underwent hysterectomy ± adjuvant treatment in SEER, National Cancer Database (NCDB), the Genomics Evidence Neoplasia Information Exchange (GENIE) project (v.13.0), and eight NCI-sponsored randomized phase III clinical trials (RCTs) were studied. Hazard ratio (HR) and 95% confidence interval (CI) were estimated for cancer-related death (CRD), non-cancer death (NCD), and all-cause death.

Results. Black ($n = 4397$) vs. White ($n = 47{,}959$) patients in SEER had a HR (95% CI) of 2.04 (1.87–2.23) for CRD and 1.22 (1.09–1.36) for NCD. In NCDB, the HR (95% CI) for death in Black ($n = 13{,}468$) vs. White ($n = 155{,}706$) patients was 1.52 (1.46–1.58) dropping to 1.29 (1.23–1.36) after propensity-score matching for age, comorbidity, income, insurance, grade, stage, LVSI, and treatment. In GENIE, Black ($n = 109$) vs. White ($n = 1780$) patients had fewer *PTEN*, *PIK3R1*, *FBXW7*, *NF1*, *mTOR*, *CCND1*, and *PI3K*-pathway-related gene mutations. In contrast, *TP53* and DNA-repair-related gene mutation frequency as well as tumor mutational burden-high status were similar in Black and White patients. In RCTs, Black ($n = 187$) vs. White ($n = 2877$) patients were more likely to have advanced or recurrent disease, higher grade, worse performance status and progressive disease. Risk of death in Black vs. White patients in RCTs was 2.19 (1.77–2.71) persisting to 1.32 (1.09–1.61) after matching for grade, stage, and treatment arm while balancing age and performance status.

Conclusions. Differences exist in clinical presentation, outcomes, and molecular features in Black vs. White patients with EEC in real-world registries and RCTs. Targeted-drug development, strategies to modify social determinants, and diverse inclusion in RCTs are approaches to reduce disparities.

1. Introduction

Uterine cancer is the most common gynecologic malignancy with a prevalence of >845,000 cases in the United States (U.S.) [1]. An ongoing increase in incidence has persisted across several decades, now with >67,000 new cases in 2024 in the U.S. alone [1,2]. At least 65%–75% of uterine malignancies are endometroid endometrial adenocarcinoma (EEC) histologic subtype [3–5]. Most cases are diagnosed promptly based on postmenopausal bleeding with early stage, low grade disease characteristics which are associated with an excellent five-year overall survival (OS) [5–7]. EEC is considered to be estrogen driven and biologically heterogeneous [4,7].

It is well documented in the literature that Black patients with endometrial cancer are twice as likely to die than White patients, more likely to be diagnosed with aggressive, non-endometrioid subtypes, and that endometrial cancer has one of the largest disparities across cancer types [8–20]. Previous studies examining racial disparities in endometrial cancer typically included both EEC and non-EEC patients, with the difference in outcome largely explained by the disproportional distribution in histology [9,11–14,16–20]. However, subset analyses demonstrated that disparities persist within EEC [8,10,12].

Explanations for survival disparities are multifaceted and complex. Black patients have been reported to be less likely than their White counterparts to receive recommended and national guideline based treatments [9,21]. In contrast, health care systems with universal access to care demonstrate it is possible to reduce differences in guideline adherent treatment between Black and White patients [22]. In settings where treatments received were similar, Black endometrial cancer

patients had worse survival which may be attributed to higher risk factors and differential treatment-related outcomes [23,24]. Race is a historic political, economic and sociocultural construct integrating migration patterns and structural determinants of health with biologic attributions of inherited ancestry, physical characteristics, exposures and lifestyle to influence disease susceptibility/severity, health and survival outcomes [15,25].

We utilized a novel four-pronged approach that incorporated complementary data from the population-based Surveillance, Epidemiology, and End Results Program (SEER) [1], the hospital cancer registry-based National Cancer Database (NCDB) [26], the international clinical sequencing Genomics Evidence Neoplasia Information Exchange (GENIE) project (v.13.0) [27], and eight National Cancer Institute (NCI)-sponsored randomized phase III clinical trials (RCTs) with the Gynecologic Oncology Group (GOG)/NRG Oncology to investigate racial disparities in clinical presentation, outcomes and molecular features in Black and White patients with EEC. This strategy focused on the most common histologic subtype, EEC, leveraging the strengths and compensating for the limitations in the data sources to extend on prior investigations, fill knowledge gaps and motivate future investigational inquiry.

2. Methods

This study utilized de-identified data under protocol #14–1679 with an exempt-determination from WCG (Western Copernicus Group) Institutional Review Board.

2.1. Patients from the Surveillance, Epidemiology, and End Results Program

Black and White patients diagnosed between 2004 and 2016 with stage I-IV low-grade EEC (grade 1 or 2 tumor) or high-grade EEC (grade 3 tumor) and underwent hysterectomy were selected from the NCI SEER-18 program, a population-based cancer program covering 28% of the U.S. population [1], using International Classification of Diseases (ICD) topography codes for endometrium and uterine corpus cancers and ICD for Oncology, third edition (ICD-O-3) histology codes 8380, 8382, 8140, 8263 and 8570 [1]. Patients with an unknown grade were excluded. Stage was categorized using the American Joint Committee on Cancer (AJCC) criteria provided by the SEER. Patients with missing data in AJCC stage were excluded. Patients without primary surgery were also excluded. Overall survival (OS) was the primary clinical outcome variable available in the SEER database, with cause of death dichotomized as cancer-related death (CRD) vs. non-cancer death (NCD).

2.2. Patients from the National Cancer Database

Black and White patients diagnosed between 2004 and 2017 with stage I-IV low grade (grade 1–2) and high grade (grade 3) EEC were selected from the NCDB [26] using the SEER selection criteria. Cancer stage was categorized using the AJCC pathologic group or Collaborative Stage Site-Specific Factor 1 when the AJCC stage was missing. All study patients were required to have a hysterectomy. Patient age, comorbidity score, neighborhood income, insurance status, year of diagnosis, lymphovascular space invasion (LVSI), lymphadenectomy and adjuvant treatment were also studied. Patients with missing data in any of these covariates (except for LVSI) were excluded. See footnote for Table 1 for details regarding comorbidity scoring, classification of median neighborhood income, insurance status, LVSI, and lymphadenectomy. Adjuvant treatment included radiotherapy alone (RT), chemotherapy alone (CT) or chemoradiotherapy (CT + RT). RT was defined as the external beam radiotherapy or vaginal brachytherapy delivered to the primary or metastatic site as the first treatment course. Patients treated with radioisotopes were excluded. CT was defined as single-agent or multi-agent chemotherapy delivered as the first course of treatment. Patients who received CT with an unspecified number of agents were also included. CT + RT was defined as both RT and CT administrated as adjuvant treatment regardless of order. OS was the clinical outcome provided by the NCDB, defined as the time from diagnosis until death or last contact.

2.3. Patients from the American association for cancer research genomics, evidence, neoplasia, information, exchange project

Data for the top 50 mutated gene observed in EEC, mutations in selected genes involved in DNA-repair, *PIK3K* or angiogenesis pathways, and tumor mutational burden (TMB) assessment in tumors from Black and White patients with EEC were downloaded from the GENIE project via cBioPortal (v13.0 released in January 2023) [27]. See the footnote in Table 2 for details regarding these genes, pathways and TMB classification.

2.4. Patients from GOG/NRG oncology randomized phase III clinical trials

A pooled analysis was performed using legacy data from completed phase III RCTs in patients with stage I-IV or recurrent endometrial cancer who enrolled in one of the eight trials. Eligibility criteria, treatments, and study results for each of them have been previously published. Highlights of these RCTs are summarized in eTable 1. Age, performance status, race, histology, stage, treatment, progression-free survival (PFS) and OS were provided under an ancillary data study agreement (DSA) #37 with NRG Oncology. Black and White patients with EEC were selected for analysis. Clinical data were centrally reviewed and confirmed by GOG/NRG Oncology. PFS was defined as the duration from trial entry to the reappearance or increase of disease or death, or last contact for censored patients. OS was defined as time from trial entry to death from any cause or last contact.

2.5. Statistical analysis

SEER data was used to estimate the racial disparities in cancer-related death (CRD) and non-cancer death (NCD) using the cumulative incidence function method, with the difference between Black and White patients evaluated through the competing-risk analysis using the Fine and Gray's sub-distribution hazards model. Data from NCDB and RCTs were used to estimate differences in demographic and clinical variables between Black and White patients using Chi-square test for categorical variables or *t*-test for age. PFS or OS were estimated with Kaplan-Meier procedure. Reverse Kaplan-Meier method was used to calculate the median follow-up duration. Risk of disease progression or death were estimated in Black vs. White patients using a Cox model to estimate hazard ratio (HR) and associated 95% confidence interval (CI). Propensity-score matching (PSM) was used to adjust the confounding effects caused by covariates, with the matching cohort achieved using a nearest-neighbor algorithm [28]. In NCDB, patient age, comorbidity score, neighborhood income, insurance status, year of diagnosis, tumor grade, stage, LVSI, lymphadenectomy and adjuvant treatment were adjusted by PSM. In the RCTs, Black and White patients were matched exactly for tumor grade, stage, and treatment arm within each RCT and balanced for patient age and performance status overall using propensity scores. Standardized mean difference (SMD) was calculated to examine the balance of covariates after matching, with a value ≤10% considered as well-balanced [18,28]. Adjusted PFS or OS between Black and White patients were estimated using Kaplan-Meier procedure from the PSM NCDB cohort or exactly matched RCT cohort. Adjusted hazard ratio (aHR) for risk of disease progression or death was also estimated from the PSM NCDB cohort or exactly matched RCT cohort using a Cox model, with 95% CI derived by a bootstrapping method. Mutation rates between Black and White patients in GENIE v13.0 were compared using Fisher's exact test. Differences in average TMB count were evaluated using t-test. Subset analysis in low-grade EEC or high-grade EEC was not applied since there was no tumor grade provided by the GENIE data.

Table 1
Characteristics in Black vs. White patients with endometrioid endometrial carcinoma in the original cohort or propensity score matched cohort diagnosed between 2004 and 2017 in the National Cancer Database.

	Original Cohort			Propensity Score Matched Cohort[b]		
	White N = 155,706	Black N = 13,468	*p*-value[a]	White N = 13,468	Black N = 13,468	SMD (%)
	Cases (%)	Cases (%)		Cases (%)	Cases (%)	
Age (years)			<0.0001			
Mean [SD]	61.7 [10.9]	60.5 [11.2]		60.3 [11.1]	60.5 [11.2]	1.4
<50	18,108 (11.6)	2080 (15.4)		2193 (16.3)	2080 (15.4)	2.3
50–54	18,898 (12.1)	1401 (10.4)		1415 (10.5)	1401 (10.4)	0.3
55–59	29,257 (18.8)	2403 (17.8)		2404 (17.9)	2403 (17.8)	0.1
60–64	29,566 (19.0)	2692 (20.0)		2708 (20.1)	2692 (20.0)	0.3
65–69	24,407 (15.7)	2211 (16.4)		2151 (16.0)	2211 (16.4)	1.2
70–74	15,662 (10.1)	1373 (10.2)		1361 (10.1)	1373 (10.2)	0.3
75–79	10,195 (6.6)	763 (5.7)		713 (5.3)	763 (5.7)	1.6
≥80	9613 (6.2)	545 (4.1)		523 (3.9)	545 (4.1)	0.8
Comorbidity Score[c]			<0.0001			
0	116,871 (75.1)	9152 (68.0)		9078 (67.4)	9152 (68.0)	1.1
≥1	38,835 (24.9)	4318 (32.1)		4390 (32.6)	4316 (32.1)	1.1
Neighborhood Income[d]			<0.0001			
<$40,227	22,235 (14.3)	5973 (44.4)		5960 (44.3)	5973 (44.4)	0.2
$40,227 - $50,353	34,715 (22.3)	2892 (21.5)		2955 (21.9)	2892 (21.5)	1.1
$50,354 - $63,332	38,499 (24.7)	2116 (15.7)		2130 (15.8)	2116 (15.7)	0.3
≥$63,333	60,257 (38.7)	2487 (18.5)		2423 (18.0)	2487 (18.5)	1.2
Insurance Status[e]			<0.0001			
Private	86,974 (55.9)	6206 (46.1)		6255 (46.4)	6206 (46.1)	0.7
Medicare	58,373 (37.5)	5111 (38.0)		5090 (37.8)	5111 (38.0)	0.3
Medicaid	6206 (4.0)	1373 (10.2)		1338 (9.9)	1373 (10.2)	0.9
Uninsured	4153 (2.7)	778 (5.8)		785 (5.8)	778 (5.8)	0.2
Year of Diagnosis			<0.0001			
2004	8481 (5.5)	633 (4.7)		597 (4.4)	633 (4.7)	1.3
2005	9202 (5.9)	609 (4.5)		609 (4.5)	609 (4.5)	0.0
2006	9917 (6.4)	765 (5.7)		805 (6.0)	765 (5.7)	1.3
2007	10,188 (6.5)	785 (5.8)		798 (5.9)	785 (5.8)	0.4
2008	10,200 (6.6)	838 (6.2)		862 (6.4)	838 (6.2)	0.7
2009	10,134 (6.5)	896 (6.7)		873 (6.5)	896 (6.7)	0.7
2010	12,336 (7.9)	983 (7.3)		952 (7.1)	983 (7.3)	0.9
2011	12,500 (8.0)	1081 (8.0)		1066 (7.9)	1081 (8.0)	0.4
2012	11,661 (7.5)	1031 (7.7)		1052 (7.8)	1031 (7.7)	0.6
2013	12,042 (7.7)	1069 (7.9)		1097 (8.2)	1069 (7.9)	0.8
2014	12,250 (7.9)	1153 (8.6)		1153 (8.6)	1153 (8.6)	0.0
2015	12,339 (7.9)	1152 (8.6)		1187 (8.8)	1152 (8.6)	0.9
2016	12,459 (8.0)	1229 (9.1)		1208 (9.0)	1229 (9.1)	0.5
2017	11,997 (7.7)	1244 (9.2)		1209 (9.0)	1244 (9.2)	0.9
Tumor Grade			<0.0001			
G1	83,185 (53.4)	5874 (43.6)		5957 (44.2)	5874 (43.6)	1.2
G2	51,849 (33.3)	4558 (33.8)		4554 (33.8)	4558 (33.8)	0.1
G3	20,672 (13.3)	3036 (22.5)		2957 (22.0)	3036 (22.5)	1.4
Stage			<0.0001			
I	128,830 (82.7)	10,584 (78.6)		10,926 (81.1)	10,584 (78.6)	6.3
II	9049 (5.8)	985 (7.3)		874 (6.5)	985 (7.3)	3.3
III	14,731 (9.5)	1451 (10.8)		1304 (9.7)	1451 (10.8)	3.6
IV	3096 (2.0)	448 (3.3)		364 (2.7)	448 (3.3)	3.6
LVSI[f]			<0.0001			
No	75,354 (48.4)	6805 (50.5)		7007 (52.0)	6805 (50.5)	3.0
Yes	14,793 (9.5)	1455 (10.8)		1300 (9.7)	1455 (10.8)	3.8
Unknown	65,559 (42.1)	5208 (38.7)		5161 (38.3)	5208 (38.7)	0.7
Lymphadenectomy[g]			0.405			
No	48,194 (31.0)	4122 (30.6)		4030 (29.9)	4122 (30.6)	1.5
Yes	107,512 (69.1)	9346 (69.4)		9438 (70.1)	9346 (69.4)	1.5
Adjuvant Treatment			<0.0001			
None	110,664 (71.1)	9083 (67.4)		9373 (69.6)	9083 (67.4)	4.6
RT alone	28,484 (18.3)	2524 (18.7)		2386 (17.7)	2524 (18.7)	2.7
CT alone	6103 (3.9)	825 (6.1)		751 (5.6)	825 (6.1)	2.3
CT + RT	10,455 (6.7)	1036 (7.7)		958 (7.1)	1036 (7.7)	2.2

Abbreviations: Lymphovascular space invasion (LVSI), Radiotherapy (RT), Chemotherapy (CT), Standardized Mean Difference (SMD).

[a] Differences in patient characteristics between the two treatment groups were compared using *Chi*-square test for categorical variables or t-test for age.

[b] Propensity-score matching was applied to balance the distribution of characteristics between Black and White patients using a nearest-neighbor algorithm adjusting for age, co-morbidity score, neighborhood income, insurance status, year of diagnosis, tumor grade, stage, LVSI, lymphadenectomy and adjuvant treatment. Standardized mean difference (SMD) was calculated to examine the balance, with a value of 10% or less considered as well-balance.

[c] Comorbidity score was coded by the National Cancer Database (NCDB) using the Charlson-Deyo index system (PMID: 1607900) and for this study was categorized as 0 or ≥ 1 (https://www.facs.org). This scoring system considers the following conditions to be a level 1: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes; level 2 consists of diabetes with chronic complications, hemiplegia or paraplegia, and renal disease; level 3 consists of moderate or severe liver disease; level 6 consists of acquired immunodeficiency syndrome. A zero score indicates the patient had none of the conditions in the Charlson-Deyo index mapping levels; however, the patients could have other co-morbid conditions.

[d] Neighborhood income was measured using the median household income for each patient's area of residence estimated by matching the five-digit zip code of the patient recorded at the time of diagnosis against files derived from the 2016 *American Community Survey* data and categorized as quartiles based on equally proportioned income ranges among all US zip codes: <$40,227, $40,227–$50,353, $50,354–$63,332 or ≥ $63,333 (https://www.facs.org).

[e] Insurance status indicated the primary insurance carrier at the time of diagnosis, and was classified as private insurance, Medicare, Medicaid or uninsured.

[f] LVSI was categorized as no, yes or unknown; since this item was not collected prior 2010, all the cases diagnosed during 2004–2009 were treated as LVSI unknown.

[g] Lymphadenectomy indicated the removal, biopsy, or aspiration of regional lymph node(s) at surgery and was categorized as no or yes.

3. Results

3.1. Clinical disparities in Black and White endometrioid endometrial cancer patients in SEER

Age and stage distribution for White and Black patients with EEC are illustrated in Fig. 1A and Fig. 1B, respectively. Black patients were diagnosed an average of 2 years younger than White patients (60.2 vs. 62.0 years old, $p < 0.0001$, respectively). Black patients were more likely to be diagnosed with stage III-IV disease than White patients (15.3% vs. 11.8%, $p < 0.0001$, respectively). Cumulative incidence of CRD and NCD were estimated in 47,959 White and 4397 Black patients in SEER and displayed in Fig. 1C and Fig. 1D, respectively. Within these 52,356 EEC patients, 7464 patients had died (52% CRD and 48% NCD). Black patients had a 2-fold higher risk for CRD (HR = 2.04, 95% CI = 1.87–2.23, $p < 0.0001$; Fig. 1E) and a 22% higher risk of NCD (HR = 1.22, 95% CI = 1.09–1.36, $p = 0.0007$; Fig. 1F) compared with White patients. Fig. 1G illustrates a 2-fold higher 5-year CRD rate (14.4% vs 7.2%) and a more modest increase in 5-year NCD rate (6.3% vs. 4.6%) between Black vs. White patients, respectively.

Black vs. White patients with low-grade EEC had increased risks for both CRD (HR = 1.71, 95% CI = 1.49–1.96, $p < 0.0001$) and NCD (HR = 1.21, 95% CI = 1.06–1.39, $p = 0.005$) whereas those with high-grade EEC had a higher risk in CRD (HR = 1.53, 95% CI = 1.36–1.72, $p < 0.0001$) but not in NCD (HR = 1.06, 95% CI = 0.85–1.31, $p = 0.616$).

3.2. Clinical presentation and survival disparities in Black and White endometrioid endometrial cancer patients in NCDB

Table 1 displays the characteristics for the 169,174 patients with EEC in NCDB, including 155,706 White and 13,468 Black patients. Black patients were younger at diagnosis, more likely than White patients to have a higher comorbidity score, live in a low-income neighborhood, and receive Medicaid insurance coverage or to be uninsured. Black patients were also significantly more likely to be diagnosed with a high-grade (G3: 22.5% vs. 13.3%) or advanced stage EEC (stage III-IV: 14.1% vs. 11.5%). As of this analysis, the median follow-up time was 79 months, and 27,958 patients had died. Estimated survival at 5-years was 81% in Black patients vs. 88% in White patients, with Black patients having a 52% higher risk of death (HR = 1.52, 95% CI = 1.46–1.58, $p < 0.0001$; Fig. 2A).

PSM analysis was conducted to adjust for all clinical covariates in Table 1 with a SMD <7% showing that the matched cohort of 13,486 Black and 13,468 White patients were well balanced. Adjusted 5-year OS was 81% in the PSM-Black patients compared to 86% in PSM-White patients, corresponding to a 29% increase in the adjusted risk of death (aHR = 1.29, 95% CI = 1.23–1.36, $p < 0.0001$; Fig. 2B).

3.3. Molecular disparities in Black and White endometrioid endometrial cancer patients in GENIE

In GENIE v13.0, there were 109 Black and 1780 White patients with EEC with available somatic mutation data. Mutations in *PTEN* (62% vs. 72%), *PIK3R1* (25% vs. 35%), *FBXW7* (6% vs. 14%), *NF1* (5% vs. 14%), *mTOR* (6% vs. 13%), *CCND1* (3% vs. 9%), and *PI3K* pathway related genes (84% vs. 92%) were significantly lower among Black vs. White patients (Fig. 2C). Mutation frequencies in 44 of the 50 top mutated genes did not vary significantly between Black and White patients (Table 2) including but not limited to *ARID1A* (54% vs. 58%), *PIK3CA* (51% vs. 52%), *CTNNB1* (29% vs. 27%), *KRAS* (21% vs. 26%), *TP53* (21% vs. 18%), *ATM* (9% vs. 15%), *FGFR2* (8% vs. 15%), *POLE* (8% vs. 13%), *MSH6* (8% vs. 11%), *BRCA2* (9% vs. 11%), and *ATR* (5% vs. 11%) (Fig. 2C).

In addition, mutation frequencies in DNA repair pathway genes and angiogenesis pathway genes were similar in Black and White patients (Fig. 2C). Somatic mutations in *MLH1*, *MSH2*, and *PMS2* were included in the DNA repair pathway gene mutation analysis but were not frequent enough to be part of the analysis of the top 50 mutated genes.

Table 2 also illustrates that Black patients had significantly lower average TMB count than White patients (22.3/Mb vs. 31.1/Mb, $p = 0.021$); however, the proportion with TMB-high did not vary by race (49% vs. 53%, $p = 0.371$).

3.4. Clinical disparities in Black and White endometrioid endometrial cancer patients in RCTs

Table 3 shows the clinical characteristics in the 2877 White and 187 Black patients with EEC enrolled in the eight NCI-sponsored RCTs. Mean age was comparable for Black vs. White patients (62 vs. 61 years, $p = 0.592$). Black patients were more likely than White patients to have worse performance status (35% vs. 23%, $p < 0.0001$), higher grade (G3: 42% vs. 21%, $p < 0.0001$), and advanced (stage III-IV) or recurrent stage (48% vs. 36%, $p = 0.0002$). There were 2142 patients who recurred, progressed, or died with a median follow-up of 61-months. Fig. 3 shows racial differences in PFS and OS. Black patients had significantly worse PFS (5-year PFS: 45% vs. 67%; HR = 2.05, 95% CI = 1.67–2.52, $p < 0.0001$; Fig. 3A) and OS (5-years OS: 48% vs. 72%; HR = 2.19, 95% CI = 1.77–2.71, $p < 0.0001$; Fig. 3B) than White patients.

Additionally, Table 3 displays the exact matching for tumor grade, stage, and treatment arm while balancing for age and performance status in 183 matched Black and White patients. Black patients had marginally worse PFS (Fig. 3C, aHR = 1.22, 95% CI = 0.99–1.50, $p = 0.064$) and significantly worse OS (Fig. 3D, aHR = 1.32, 95% CI = 1.09–1.61, $p = 0.006$) compared with matched White patients.

4. Discussion

We identified disparities in clinical characteristics, outcomes, and molecular alterations between Black and White women with EEC based on real-world data and/or NCI-sponsored RCTs. This multipronged approach was a novel component of this investigation. In our SEER evaluation of surgically managed patients, 5-year survival was 79% vs. 88% in Black vs. White patients with EEC with 70% vs. 61% of the deaths related to cancer, respectively. The disparity was 2-fold higher in CRD and only 22% larger in NCD. Moreover, we confirmed that Black vs. White patients in SEER with low-grade EEC had increased risks for both CRD and NCD whereas those with high-grade EEC had a higher risk in CRD but not in NCD. In contrast, the prior SEER studies often included all patients independent of surgical management with all uterine or endometrial cancer histologic subtypes and reported on different endpoints. For example, Sud et al. [9] performed Cox modeling and competing risk survival analyses in Black and White patients with type I endometrial cancer (EEC, adenocarcinoma, and mucinous subtypes), type II endometrial cancer (clear cell, serous and anaplastic subtypes), or sarcoma in Black vs. White patients showing that Black patients had worse OS and cancer-specific mortality and were less likely to undergo surgery. Tarney et al. [10] showed the impact of age on proportion with EEC vs. non-EEC histology, OS and cancer-specific survival in Black vs. White patients. Clarke et al. [11,13] reported that Black patients had higher hysterectomy-corrected incidence and mortality rates per 100,000 individuals as well as worse 5-year OS than White, Asian, or Hispanic patients with EEC or non-EEC histology. The definition of EEC utilized by Clarke et al. [11,13] also included cystadenocarcinoma, mucinous carcinoma and adenosquamous carcinoma.

Our analysis in NCDB utilized propensity score matching of clinical covariates including demographics, geographic region, socioeconomic factors, medical comorbidities, and insurance which are not readily available in traditional SEER studies or NCI-sponsored RCTs but may be present in SEER-Medicaid studies. This study extends on our recent NCDB study by Kucera et al. [18] which utilized a sequential propensity

Table 2
Mutations in selected genes and pathways in White vs. Black patients with endometrioid endometrial carcinoma in GENIE v13.0.

Top 50 Mutated Genes[a]	White Patients		Black Patients		*p*-value
	Cases	Cases with Mutations (%)	Cases	Cases with Mutations (%)	
PTEN	**1780**	**1287 (72.3)**	**109**	**68 (62.4)**	**0.029**
PIK3R1	**1703**	**597 (35.1)**	**103**	**26 (25.2)**	**0.043**
NF1	**1702**	**236 (13.9)**	**103**	**5 (4.9)**	**0.007**
FBXW7	**1780**	**246 (13.8)**	**109**	**7 (6.4)**	**0.029**
mTOR	**1694**	**216 (12.8)**	**103**	**6 (5.8)**	**0.043**
CCND1	**1693**	**152 (9.0)**	**103**	**3 (2.9)**	**0.029**
ARID1A	1693	986 (58.2)	103	56 (54.4)	0.472
PIK3CA	1780	921 (51.7)	109	56 (51.4)	1.000
CTNNB1	1780	471 (26.5)	109	32 (29.4)	0.504
KRAS	1780	465 (26.1)	109	23 (21.1)	0.262
KMT2D	1678	430 (25.6)	103	29 (28.2)	0.563
CTCF	1449	371 (25.6)	96	24 (25.0)	1.000
ZFHX3	1117	284 (25.4)	80	23 (28.8)	0.509
KMT2B	1032	259 (25.1)	77	14 (18.2)	0.217
BCOR	1678	320 (19.1)	103	20 (19.4)	0.898
INPPL1	901	170 (18.9)	72	15 (20.8)	0.642
TP53	1780	317 (17.8)	109	23 (21.1)	0.371
FAT1	1382	237 (17.2)	90	11 (12.2)	0.248
JAK1	1474	231 (15.7)	96	17 (17.7)	0.565
ATM	1770	271 (15.3)	109	10 (9.2)	0.096
ARID1B	1611	244 (15.2)	97	18 (18.6)	0.383
FGFR2	1780	264 (14.8)	109	9 (8.3)	0.067
RNF43	1474	213 (14.5)	96	13 (13.5)	0.882
KMT2C	1184	164 (13.9)	87	9 (10.3)	0.421
MED12	1464	189 (12.9)	96	15 (15.6)	0.435
POLE	1421	183 (12.9)	94	7 (7.5)	0.147
NSD1	1442	177 (12.3)	94	13 (13.8)	0.628
MGA	1332	159 (11.9)	83	10 (12.1)	1.000
NOTCH3	1408	165 (11.7)	92	8 (8.7)	0.500
ATRX	1693	198 (11.7)	103	6 (5.8)	0.077
SPEN	1227	139 (11.3)	91	13 (14.3)	0.395
KMT2A	1693	190 (11.2)	103	9 (8.7)	0.520
CREBBP	1693	186 (11.0)	103	11 (10.7)	1.000
APC	1765	190 (10.8)	109	8 (7.3)	0.334
MSH6	1703	182 (10.7)	103	8 (7.8)	0.411
SETD2	1693	181 (10.7)	103	7 (6.8)	0.248
ATR	1464	157 (10.7)	96	5 (5.2)	0.117
BRCA2	1726	182 (10.5)	106	9 (8.5)	0.623
MAP3K1	1678	174 (10.4)	103	9 (8.7)	0.738
ERBB3	1703	177 (10.4)	103	7 (6.8)	0.313
EP300	1678	168 (10.0)	103	13 (12.6)	0.400
NOTCH1	1780	178 (10.0)	109	9 (8.3)	0.740
CIC	1449	144 (9.9)	96	7 (7.3)	0.480
ROS1	1693	167 (9.9)	103	5 (4.9)	0.118
SMARCA4	1693	161 (9.5)	103	8 (7.8)	0.724
DICER1	1668	157 (9.4)	101	7 (6.9)	0.483
NFE2L2	1693	150 (8.9)	103	5 (4.9)	0.205
PTCH1	1693	146 (8.6)	103	9 (8.7)	1.000
ASXL1	1693	144 (8.5)	103	6 (5.8)	0.462
RB1	1780	148 (8.3)	109	6 (5.5)	0.369
	White Patients		**Black Patients**		
	Cases	**Cases with Mutations (%)**	**Cases**	**Cases with Mutations (%)**	***p*-value**
DNA Repair Pathway[b]	1780	729 (41.0)	109	43 (39.5)	0.841
***PI3K* Pathway**[c]	**1780**	**1640 (92.1)**	**109**	**92 (84.4)**	**0.011**
Angiogenesis Pathway[d]	1780	126 (7.1)	109	5 (4.6)	0.436
Tumor Mutational Burden[e]					
TMB-High	1743	927 (53.2)	107	52 (48.6)	0.371
Mean ± SD	**1743**	**31.12 ± 72.06**	**107**	**22.27 ± 34.86**	**0.021**
Median [IQR]	1743	10.0 [6.0–29.0]	107	9.0 [5.0–28.0]	

Analysis conducted based on the American Association of Cancer Research (AACR) Genomics Evidence Neoplasia Information Exchange (GENIE) project (v.13.0) database.
Difference by race evaluated by Fisher's exact test for mutation rate or by t-test for tumor mutational burden (TMB) with significant differences **bolded**.

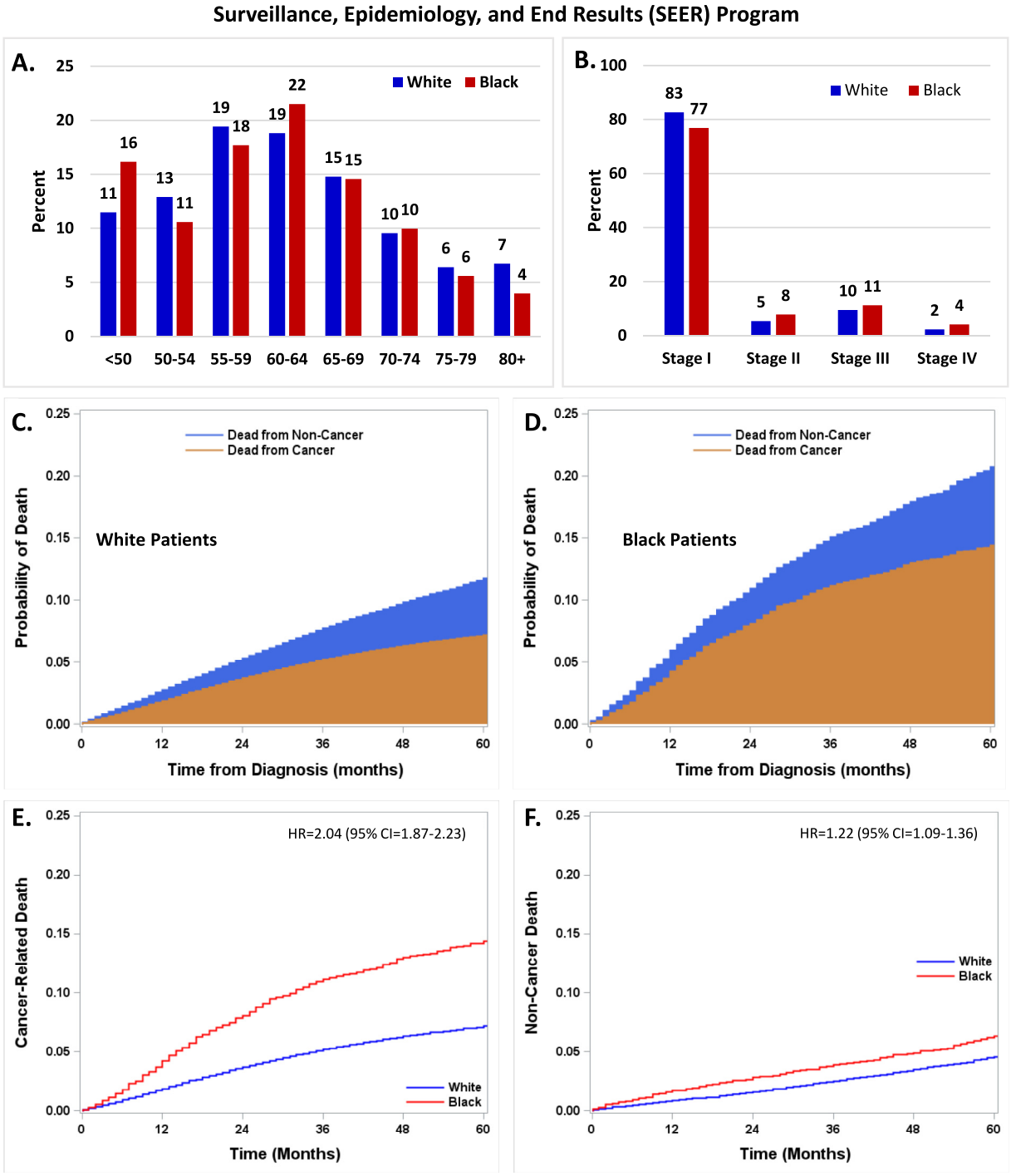
[a] Top 50 most frequently mutated gene in endometrioid endometrial carcinoma in GENIE v13.0.

[b] DNA-Repair pathway alteration defined based on 25 genes (*ERCC2, ERCC5, ERCC4, POLE, MSH2, MLH1, MSH6, PMS2, PMS1, BARD1, NBN, BRCA2, RAD50, PALB2, BRCA1, RAD21, RAD52, FANCA, FANCC, ATM, ATR, CHEK1, CHEK2, MDC1, PARP1*), with any mutation in any of these genes defined as DNA-repair pathway alteration.

[c] *PIK3K* pathway alteration defined based on 22 genes (*AKT1, AKT2, AKT3, INPP4B, MLST8, MTOR, NPRL2, NPRL3, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIK3R3, PPP2R1A, PTEN, RHEB, RICTOR, RPTOR, RPS6KB1, STK11, TSC1, TSC2*) with any mutation in any of these genes defined as *PIK3* pathway alteration.

[d] Angiogenesis pathway based on 6 genes (*VEGFA, VEGFB, KDR, CXCL8, CXCR1, CXCR2*) with any alteration in any of these genes defined as angiogenesis pathway alteration.

[e] TMB indicating total number of mutations per Mb, with TMB-high defined as 10 or more mutations per Mb.



G.

	Total Cases	Cancer Related Deaths (CRD)				Non-Cancer Deaths (NCD)			
		CRD	5-Yr CRD %	HR (95% CI)	*p*-value	NCD	5-Yr NCD %	HR (95% CI)	*p*-value
White	47,959	3,333	7.2	Reference		3,221	4.6	Reference	
Black	4,397	577	14.4	2.04 (1.87-2.23)	<0.0001	333	6.3	1.22 (1.09 – 1.36)	0.0007

Fig. 1. Surgically managed Black and White patients diagnosed between 2004 and 2016 with stage I-IV low-grade (grade 1–2 tumor) or high-grade (grade 3 tumor) endometrioid endometrial cancer from the National Cancer Institute's SEER-18 registries. Bar graphs showing the distribution of Black vs. White patients by age at diagnosis (A) or stage of disease (B). Probability of cancer-related and non-cancer death in White (C) or Black patients (D). Racial disparities in cumulative incidence of cancer-related deaths (E) or non-cancer deaths (F) for Black vs. White patients. Table displaying the number of patients and deaths, 5-year cancer-related death (CRD) or non-cancer death (NCD) rates and hazard ratio (HR) and 95% confidence interval (CI) for CRD or NCD in White vs. Black patients (G).

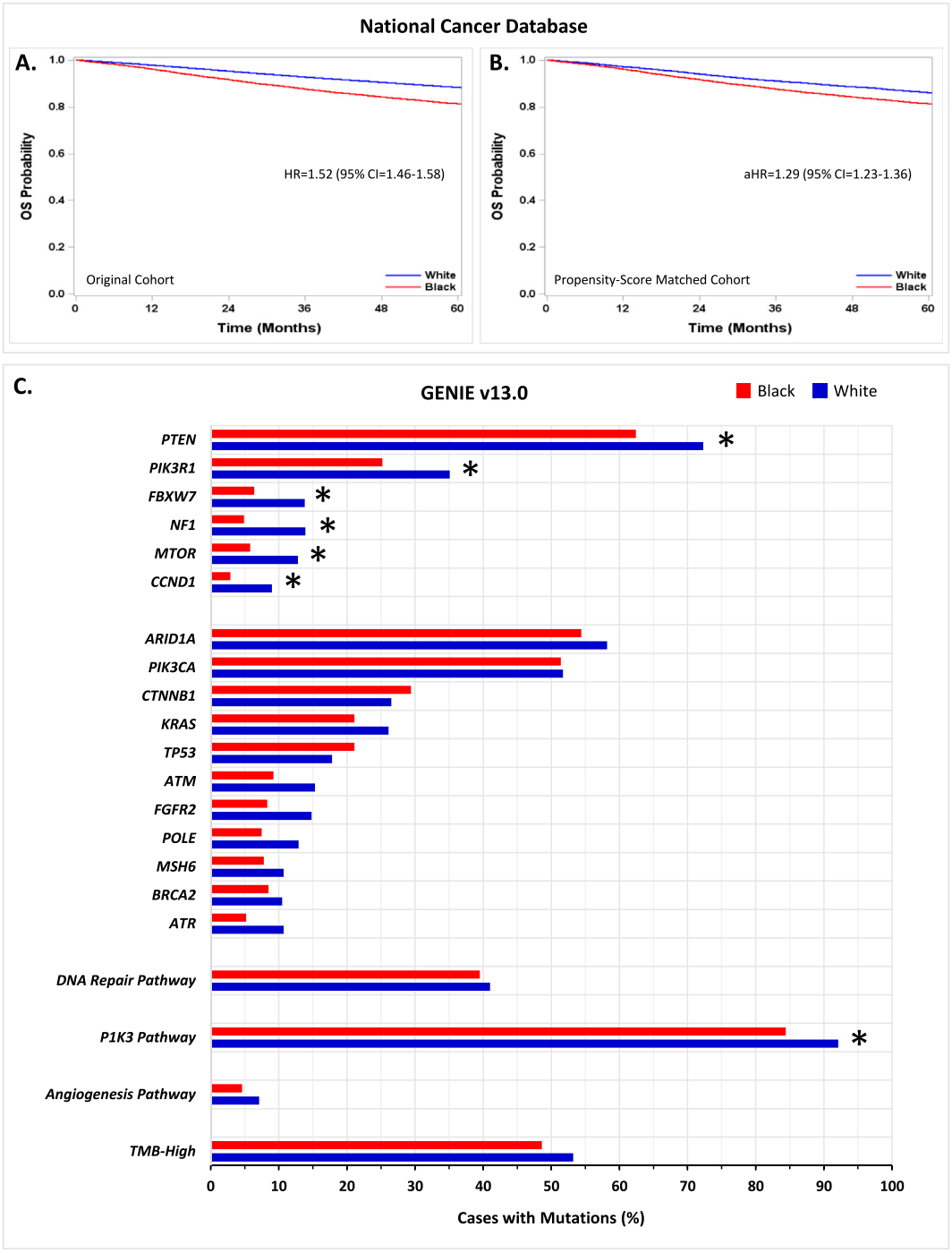


Fig. 2. Overall survival (OS) in Black vs. White patients diagnosed between 2004 and 2017 with stage I-IV low grade (grade 1–2) and high grade (grade 3) endometrioid endometrial cancer in the original cohort (A) and propensity-score matched cohort (B) in the National Cancer Database. Propensity score matching analysis adjusted for patient age, comorbidity score, neighborhood income, insurance status, year of diagnosis, tumor grade, stage, LVSI, lymphadenectomy and adjuvant treatment. Hazard ratio (HR) or adjusted HR (aHR) and 95% confidence interval (CI) for risk of death were estimated from Cox modeling. Bar graph (C) displays the mutation frequency in selected genes and pathways for Black vs. White patients with endometrioid endometrial cancer in GENIE v13.0. Difference by race were evaluated by Fisher's exact test for somatic mutations or by *t*-test for tumor mutational burden (TMB) with significant differences ($p < 0.05$) highlighted with an Asterix. TMB indicating total number of mutations per Mb, with TMB-high defined as 10 or more mutations per Mb.

score weighting approach to demonstrate that 54.1% of the survival difference between Black and White patients was explained by histology and 17.7% remained unexplained after correcting for age, census division, year of diagnosis, comorbidity score, neighborhood income, insurance status, histology by grade, stage, and first-line treatment (surgery, radiotherapy, chemotherapy). In this present NCDB analysis, we show that a large portion of Black patients who died had higher grade, advanced stage, or both. In 2016, Fader et al. [21] used NCDB to study endometrioid, clear cell or serous carcinoma in all racial and ethnic groups and showed that Black race, socioeconomic factors, geographic region and facility-related factor were associated with advanced stage IIIC/IV disease and Black women had the worst OS even after performing multivariate modeling. In 2017, Bregar et al. [24] used NCDB to exclusively study high-grade endometrial cancers and show that stage,

Table 3
Characteristics in Black vs. White patients with endometrioid endometrial carcinoma in the original cohort or matched cohort enrolled between 1988 and 2013 in NCI-sponsored Gynecologic Oncology Group (GOG)/NRG Oncology randomized phase III clinical trials.

	Original Cohort		Matched Cohort[a]		
	White N = 2877	Black N = 187	White N = 183	Black N = 183	**SMD (%)**
	Cases (%)	Cases (%)	Cases (%)	Cases (%)	
Age (years)					
Mean ± SD (standard deviation)	61.4 ± 10.7	61.9 ± 10.5	62.2 ± 9.4	62.1 ± 10.5	1.4
<50	349 (12.1)	19 (10.2)	16 (8.7)	18 (9.8)	3.8
50–54	384 (13.4)	22 11.8)	22 (12.0)	20 (10.9)	3.4
55–59	553 (19.2)	24 (12.8)	26 (14.2)	24 (13.1)	3.2
60–64	479 (16.7)	44 (23.5)	42 (23.0)	43 (23.5)	1.3
65–69	425 (14.8)	31 (16.6)	31 (16.9)	31 (16.9)	0.0
70–74	317 (11.0)	34 (18.2)	33 (18.0)	34 (18.6)	1.4
75–79	259 (9.0)	9 (4.8)	9 (4.9)	9 (4.9)	0.0
≥80	111 (3.9)	4 (2.1)	4 (2.2)	4 (2.2)	0.0
Performance Status					
0	2221 (77.2)	121 (64.7)	126 (68.9)	119 (65.0)	8.1
≥1	665 (22.8)	66 (35.3)	57 (31.2)	64 (35.0)	8.1
Tumor Grade					
G1	1110 (38.6)	45 (24.1)	44 (24.0)	44 (24.0)	0.0
G2	1151 (40.0)	64 (34.2)	63 (34.4)	63 (34.4)	0.0
G3	616 (21.4)	78 (41.7)	76 (41.5)	76 (41.5)	0.0
Stage					
I	1724 (59.9)	87 (46.5)	86 (47.0)	86 (47.0)	0.0
II	123 (4.3)	10 (5.4)	10 (5.5)	10 (5.5)	0.0
III	473 (16.4)	29 (15.5)	27 (14.8)	27 (14.8)	0.0
IV	164 (5.7)	15 (8.0)	14 (7.7)	14 (7.7)	0.0
Recurrent (R)	393 (13.7)	46 (24.6)	46 (25.1)	46 (25.1)	0.0
Randomized Phase III Clinical Trials					
GOG-0107 [1988–1992] {Stage III-IV, R}[b]					
Doxorubicin	58 (2.0)	8 (4.3)	8 (4.4)	8 (4.4)	0.0
Doxorubicin/Cisplatin	49 (1.7)	7 (3.7)	6 (3.3)	6 (3.3)	0.0
GOG-0122 [1992–2000] {Stage III-IV}[c]					
Whole Abdominal Irradiation	86 (3.0)	10 (5.4)	10 (5.5)	10 (5.5)	0.0
Doxorubicin/Cisplatin	74 (2.6)	10 (5.4)	10 (5.5)	10 (5.5)	0.0
GOG-0139 [1993–1996] {Stage III-IV, R}[d]					
Doxorubicin/Cisplatin (standard)	65 (2.3)	11 (5.9)	9 (4.9)	9 (4.9)	0.0
Doxorubicin/Cisplatin (circadian)	68 (2.4)	5 (2.7)	5 (2.7)	5 (2.7)	0.0
GOG-0163 [1996–1998] {Stage III-IV, R}[e]					
Doxorubicin/Cisplatin	67 (2.3)	4 (2.1)	4 (2.2)	4 (2.2)	0.0
Doxorubicin/Paclitaxel	64 (2.2)	11 (4.8)	9 (4.9)	9 (4.9)	0.0
GOG-2222 (LAP-2) [1996–2005] {Stage I-IIA}[f]					
Laparoscopy	983 (34.2)	38 (20.3)	38 (20.9)	38 (20.9)	0.0
Laparotomy	551 (19.2)	20 (10.7)	20 (10.9)	20 (10.9)	0.0
GOG-0177 [1998–2000] {Stage III-IV, R}[g]					
Doxorubicin/Cisplatin	76 (2.6)	6 (3.2)	6 (3.3)	6 (3.3)	0.0
Doxorubicin/Cisplatin/Paclitaxel	70 (2.4)	10 (5.4)	10 (5.5)	10 (5.5)	0.0
GOG-0184 [2000–2004] {Stage III-IV}[h]					
Doxorubicin/Cisplatin	165 (5.7)	7 (3.7)	7 (3.8)	7 (3.8)	0.0
Doxorubicin/Cisplatin/Paclitaxel	188 (6.5)	3 (1.6)	3 (1.6)	3 (1.6)	0.0
GOG-0249 [2009–2013] {Stage I-II}[i]					
Pelvic Radiation therapy	156 (5.4)	17 (9.1)	16 (8.7)	16 (8.7)	0.0
Brachytherapy + Carboplatin/Paclitaxel	157 (5.5)	22 (11.8)	22 (12.0)	22 (12.0)	0.0

[a] Black and White patients with endometrioid endometrial carcinoma in the randomized clinical trials were matched exactly for tumor grade, stage, and treatment arm within each randomized clinical trial and balanced for patient age and performance status using propensity scores. Standardized mean difference (SMD) was calculated to examine the balance, with a value of 10% or less considered as well-balance.

[b] GOG-0107, Phase III Trial of Doxorubicin With or Without Cisplatin in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study [Doxorubicin 60 mg/m^2 vs Doxorubicin 60 mg/m^2 and Cisplatin 50 mg/m^2] PMID: 15459211.

[c] GOG-0122, Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study [Whole-abdominal irradiation vs Doxorubicin 60 mg/m^2 and Cisplatin 50 mg/m^2] PMID: 16330675.

[d] GOG-0139, Randomized phase III trial of standard timed Doxorubicin plus Cisplatin versus circadian timed Doxorubicin plus Cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study [Doxorubicin 60 mg/m^2 over 30 min, and Cisplatin 60 mg/m^2 over 30 min (standard) vs Doxorubicin 60 mg/m^2 over 30 min at 6 am and Cisplatin 60 mg/m^2 over 30 min at 6 pm (circadian)] PMID: 14551299.

[e] GOG-0163, Phase III randomized trial of Doxorubicin + Cisplatin versus Doxorubicin +24-h Paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study [Doxorubicin 60 mg/m^2 and Cisplatin 50 mg/m^2 vs Doxorubicin 50 mg/m^2 and Paclitaxel 150 mg/m^2 (with G-CSF)] PMID: 15277255.

[f] GOG-2222, Laparoscopy Compared With Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group Study LAP2 [Laparotomy vs Laparoscopy] PMID: 19805679.

[g] GOG-0177, Phase III trial of Doxorubicin plus Cisplatin with or without Paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study [Doxorubicin 60 mg/m^2 and Cisplatin 50 mg/m^2 vs Doxorubicin 45 mg/m^2, Cisplatin 50 mg/m^2, and Paclitaxel 160 mg/m^2 (with G-CSF)] PMID: 15169803.

[h] GOG-0184, A Randomized Phase III Trial in Advanced Endometrial Carcinoma of Surgery and Volume Directed Radiation Followed by Cisplatin and Doxorubicin with or without Paclitaxel: A Gynecologic Oncology Group Study [Doxorubicin 45 mg/m^2 and Cisplatin 50 mg/m^2 IV (with G-CSF) vs Doxorubicin, Cisplatin, and Paclitaxel 160 mg/m^2 (with G-CSF)] PMID: 19108877.

[i] GOG-0249, A Phase III Trial of Pelvic Radiation Therapy Versus Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin Chemotherapy in Patients With High Risk, Early Stage Endometrial Carcinoma [Pelvic Radiation vs Vaginal Brachytherapy plus Carboplatin AUC6 and Paclitaxel 175 mg/m^2] PMID: 30995174.

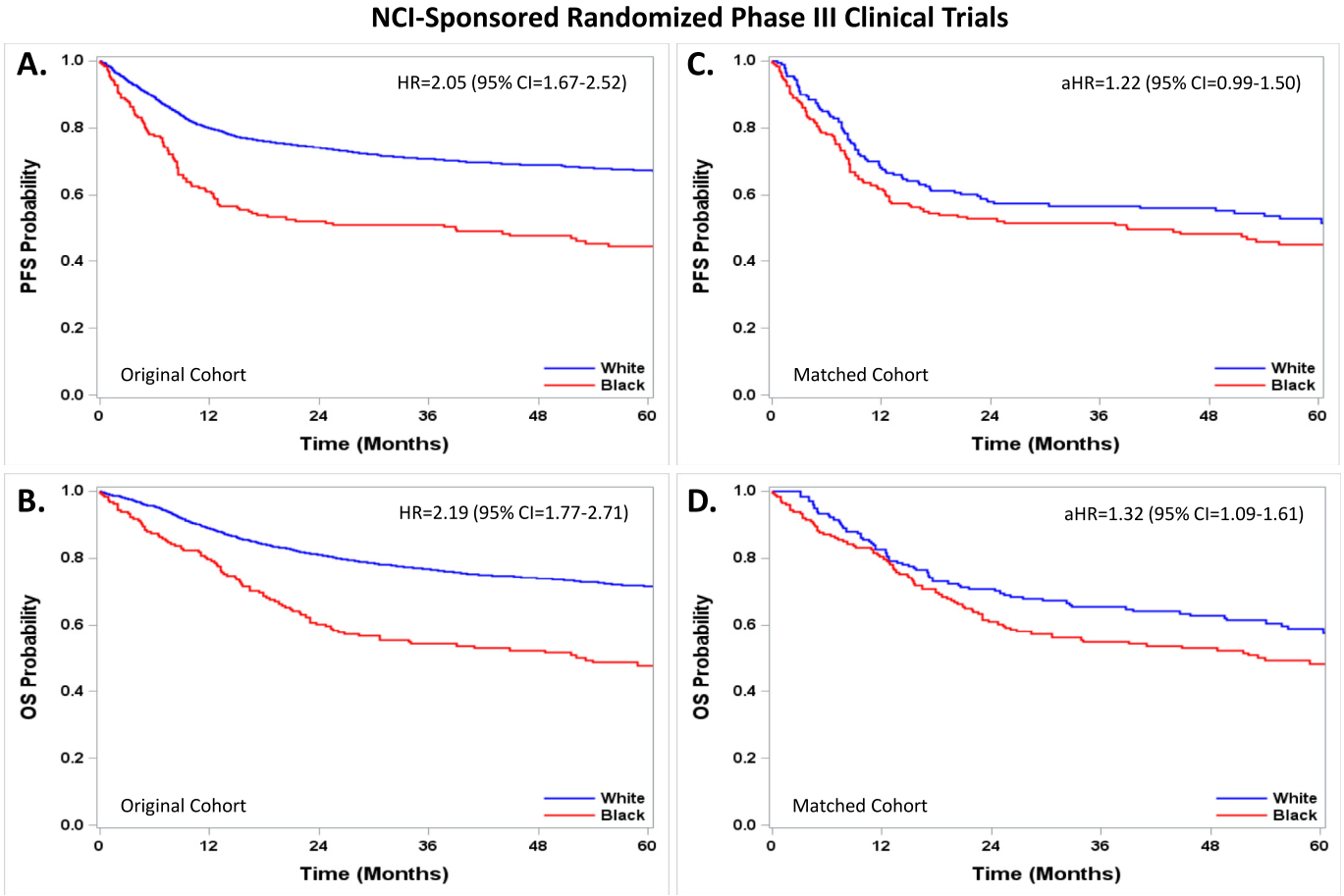


Fig. 3. A pooled analysis in eight NCI-sponsored randomized phase III clinical trials (RCTs) in patients with stage I-IV or recurrent endometrioid endometrial cancer. Highlights of these RCTs are summarized in Table 2 and eTable 1. Progression-free survival (PFS, A, C) and overall survival (OS, B, D) in Black vs. White patients in the original cohort (A, B) or the matched cohort (C, D) after exactly matching for tumor grade, stage and treatment arm and balancing for age and performance based on propensity scores. Hazard ratio (HR) or adjusted HR (aHR) and 95% confidence interval (CI) for risk of disease progression or death were estimated from Cox modeling.

grade, and surgical status alone account for a significant portion of disparities between outcomes of Black and White patients. While the survival difference in our study may initially be attributed to the grade and stage of these patients, once PSM was performed to mitigate the confounding from stage and grade as well as socioeconomic status among other variables, we found persistent survival differences with a nearly 29% adjusted increased risk of death in Black patients. The persistent disparities suggest the involvement of other factors, including access and barriers to care, ancestry, exposures, lifestyle, and social determinants of health as we were unable to account for these in our PSM.

Inclusion of data from eight completed phase III RCTs allowed us to compare progression-free and overall survival in exactly matched and propensity-score balanced Black vs. White patients with histologically confirmed EEC treated and followed in a standardized manner with centralized study chair and modality reviews which was not possible within the individual RCTs or in traditional SEER and NCDB investigations. In our integrated analysis of eight RCTs, Black patients were more likely to have worse performance status, higher tumor grade and more advanced stage disease. After applying exact matching by tumor grade, stage, and treatment arm within each RCT and balancing age and performance status, these disparities persisted. Once again, an increased risk of death for Black patients (32%) suggests there are factors beyond income, grade, stage, comorbidities, and treatment that are driving these disparities in EEC. Chapman-Davis et al. [29] addressed this exact point in their landmark series on disparities in uterine cancer noting that "we…must not diminish the role structural racism, poverty, and implicit bias play in the USA health system overall" [29].

Our study reports racial differences in somatic mutations from the international GENIE [27] project in 109 Black and 1780 White patients with EEC. These data extend on the racial differences in molecular subtypes, common mutations and/or transcript-based expression reported across endometrial cancer histologic subtypes using the Cancer Genome Atlas (TCGA) Research Network data [8,10,30,31] and Wilhite et al. [32] using commercial molecular assessments. The TCGA studies included a subset of 28–69 Black and 249–293 White patients with ECC and the Wilhite study included a subset of 18 Black vs. 69 White patients with EEC. Herein we document mutation differences and similarities between Black and White patients with EEC that may contribute to the observed disparities or provide potential therapeutic opportunities. Our analysis reported fewer mutations in *PTEN* (62% vs. 72%), *PIK3R1* (25% vs. 35%), and *PI3K* pathway related genes (84% vs. 92%) in cancers from Black vs. White patients, making them particularly attractive molecular targets in EEC. In contrast, *NF1*, *FBXW7*, *mTOR*, and *CCND1* were less frequently mutated (<15%), but the magnitude of difference was 2- to 3-fold with potential implications for selective targeting. Similarly mutated DNA repair pathway related genes (40% vs. 41%), TMB-high status (49% vs. 53%) or *MSH6* (8% vs. 11%) genes may offer generalized opportunities for immune checkpoint inhibition [33,34]. Additional generalized molecular targeting opportunities may extend to the 21–58% of tumors with *ARID1A*, *PIK3CA*, *CTNNB1* and *KRAS* or 5–21% of tumors with *TP53*, *ATM*, *FGFR2*, *POLE*, *MSH6*, *BRCA2*, and *ATR* mutation (s). We also reported a similar frequency of *TP53* mutations between Black and White patients with EEC which varies from prior reports [10,31,32,35] showing higher *TP53* mutations in endometrial cancer

cohorts attributed in part to the inclusion of serous carcinoma and/or carcinosarcoma subtypes. See Supplementary Materials for additional references covering racial disparities in *p53* immunohistochemical staining, other molecular alterations/subtypes, outcomes, obesity, cardiovascular risk, and guideline compliant care.

We acknowledge limitations to our research. First and foremost, our study is limited by the inherent focus on a single histologic subtype in a disease that is well documented to have a higher proportion of aggressive histologic subtypes in Black vs. White patients [9,11–14,16–20]. The focus on surgically-managed EEC patients likely contributed to the lower representation of Black patients in our SEER and NCDB cohorts. The representation of Black patients in GENIE (5.8%) and these RCTs (6.1%) was even lower compared with 7.6% seen in SEER and NCDB and 13.6% reported by the U.S. Census Bureau. Additionally, we did not investigate different modalities of radiation or chemotherapy, and did not examine Hispanic, Asian, Pacific Islander, American Indian or Alaskan Native patients. We also were not able to centrally review pathology and other data within SEER or NCDB and staging varied between cohorts. While our study included several large RCTs, we were also unable to include more recently completed RCTs, such as those investigating newer agents such as immune-checkpoint inhibitors, molecular targeting agents, antibody drug conjugate, as well as in combinations with traditional cytotoxic chemotherapy. We minimized the confounding effects of covariates in NCDB using PSM and in RCTs by exactly matching tumor grade, stage, and treatment with each RCT and balancing age and performance status.

Additionally, self-reported race is a historic political, economic and social construct that often simplifies highly complex ancestry with migration patterns, structural determinants of health, exposures, lifestyle, biology and sociocultural influences [15,25]. Our study was also not able to examine the roles that racism, oppression, forced migration, systems and structures play in the observed disparities between Black and White patients with EEC. Sucheston et al. [36] noted that there are differences in individual ancestries within self-reported Black patients in Louisiana (Cajun, Creole or both Cajun and Creole) and North Carolina highlighting ethnic and regional diversities within Black patients likely reflective of distinct migration patterns, cultures, lifestyles, diets and exposures. Moreover, physiologic and geographic differences within racial and ethnic groups are also challenging to account for. Vishnu et al. [37] identified that U.S.-born Black people were more likely to have a higher BMI and risk of obesity compared to their European counterparts. These studies advocate that race be recognized as a heterogeneous group in terms of impact on health and outcome. Obesity at endometrial cancer diagnosis has been shown to be associated with increased cancer recurrence and OS [38]. Our study was limited by the lack of available BMI data for analysis. Kucera et al. [18] noted that simplifying race to a "White" and "Black" construct may lead to generalizations and potentially false conclusions. In light, however, of exploring a previously under-investigated area of potential disparity and the retrospective nature of the data provided from the cohorts utilized for this study, we believe that these biases were mitigated, at least in part, by our PSM and exact matching approaches. The Office of Management and Budget is currently developing an update to the two-question race and ethnicity standard established under the 1997 Statistical Policy Directive No. 15 to a single question to capture self-identified affiliation with up to seven groups and embedded country of origin details reflective of modern diversity in the U.S. The lower representation of Black patients with EEC observed in our SEER, NCDB, RCTs and GENIE cohorts is consistent with the 7.1% enrollment of Black patients reported by Montes de Oca et al. [39] in uterine cancer trials between 1988 and 2019 and well below the 13.6% representation of Black individuals reported by the U.S. Census Bureau. The GOG Foundation and Society of Gynecologic Oncology (SGO) jointly proposed IDEA initiative is advocating a multi-tiered strategy with recommendations for increasing inclusion, diversity, equity and access in gynecologic oncology clinical trials [40]. Inclusion of diverse and underrepresented participants is needed to help study and ultimately mitigate disparities and achieve equitable care and outcomes in patients with EEC.

In conclusion, our investigation highlights racial disparities in clinical characteristics, molecular alterations, and survival outcomes between Black and White women with EEC that were observed in both real-world data as well as in patients who participated in RCTs. The difference in survival remained significant even after adjusting for demographic, socioeconomic, tumor grade, stage, and treatment factors. These disparities merit additional research on molecular features, exposures, lifestyle, biology, and societal factors. Targeted-drug development, strategies to modify social determinants, and diverse inclusion in RCTs are additional approaches to reduce disparities.

Presentations

An abstract and oral presentation for this work was presented during the Society of Gynecologic Oncology Annual Meeting on Women's Cancer in San Diego, CA in March 2024.

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Disclaimer

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CRediT authorship contribution statement

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Declaration of interests

Zachary A. Kopelman, Chunqiao Tian, Jordyn Tumas, Neil T. Phippen, Christopher M. Tarney, Erica R. Hope, Stuart S. Winkler, Suzanne Jokajtys, Calen W. Kucera, Michael T. Richardson, Daniel S. Kapp, Nathaniel L. Jones, Rodney P. Rocconi, John H. Farley, Angeles Alvarez Secord, Casey M. Cosgrove, Matthew A. Powell, Ann Klopp, Joan L Walker, Gini F. Fleming, Nicholas W. Bateman, G. Larry Maxwell, and Kathleen M. Darcy do not have any conflicts to report. John K. Chan reported personal fees from Agenus, AstraZeneca, Eisai, Genmab, GlaxoSmithKline, Immunogen, Mersana, Molecular Targeting Technologies, Myriad, Roche, and Seagen outside the submitted work. Chad A. Hamilton reported personal fees from GlaxoSmithKline outside the submitted work. Charles A. Leath, III received funding from the NIH UG1 CA23330 and P50 CA098252, contracted research with GSK and Merck, and served on a scientific advisory board for GSK and Merck, all outside of the submitted work. Thomas P. Conrads is a ThermoFisher Scientific, Inc. SAB member and receives research funding from AbbVie outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.03.026.

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