Gynecologic Oncology 176 (2023) 98–105

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Intra-racial disaggregation reveals associations between nativity and overall survival in women with endometrial cancer

Alyssa J. Mercadel [a,b], Alex P. Sanchez-Covarrubias [a,b], Heidy N. Medina [c], Paulo S. Pinheiro [b,c], Andre Pinto [d], Sophia H.L. George [a,b], Matthew P. Schlumbrecht [a,b,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, Leonard M. Miller School of Medicine, University of Miami, 1121 NW 14th Street, Suite 345C, Miami, FL 33136, USA
[b] Sylvester Comprehensive Cancer Center, 1475 NW 12th Avenue, Miami, FL 33136, USA
[c] Department of Public Health Sciences, University of Miami School of Medicine, 1120 NW 14th Street, CRB 919, Miami, FL 33136, USA
[d] Department of Pathology, University of Miami Miller School of Medicine, 1611 NW 12th Avenue, Holtz 2145, Miami, FL 33136, USA

HIGHLIGHTS

- Intra-racial disaggregation provides additional insight into health disparities found in women with endometrial cancer (EC).
- Jamaican and Haitian-born Black women in the US have higher rates of high-grade EC than US-born Black women.
- Haitian-born Black women in the US with serous EC experience worse overall survival than women born in Jamaica and the US.

ARTICLE INFO

Article history:
Received 16 May 2023
Received in revised form 12 July 2023
Accepted 13 July 2023
Available online 20 July 2023

Keywords:
Endometrial cancer
Ancestry
Health disparities
Caribbean women
Black women

ABSTRACT

Objective. Prior studies have demonstrated survival differences between Black women with endometrial cancer (EC) born in the US and Caribbean. Our objective was to determine if country of birth influences EC overall survival (OS) in disaggregated subpopulations of Black women.

Methods. Using the Florida Cancer Data System, women with EC diagnosed from 1981 to 2017 were identified. Demographic and clinical information were abstracted. Women who self-identified as Black and born in the US (USB), Jamaica (JBB), or Haiti (HBB) were included. Statistical analyses were performed using chi-square, Cox proportional hazards models, and Kaplan-Meier methods with significance set at $p < 0.05$.

Results. 3817 women met the inclusion criteria. Compared to USB, JBB and HBB had more high-grade histologies, more advanced stage disease, had a greater proportion of uninsured or Medicaid insured, and had a higher proportion of women who received chemotherapy (all $p < 0.05$). In multivariate analyses, age (HR 1.03 [1.02–1.05]), regional stage (HR 1.52 [1.22–1.89]), distant stage (HR 3.73 [2.84–4.89]), lymphovascular space invasion (HR 1.96 [1.61–2.39]), receipt of surgery (HR 0.47 [0.29–0.75]), and receipt of chemotherapy (HR 0.77 [0.62–0.95]) were independently associated with OS. Compared to USB, Haitian nativity was an independent negative predictor of OS when evaluating all histologies together (HR 1.54 [1.18–2.00]) and for endometrioid EC specifically (HR 1.77 [1.10–2.83]). Among women with serous EC, HBB had markedly worse median OS (18.5 months [13.4–46.5]) relative to USB (29.9 months [26.3–35.9]) and JBB (41.0 months, [34.1–82.6], $p = 0.013$).

Conclusion. Country of birth is associated with endometrial cancer survival in Black women, with HBB demonstrating worse outcomes.

1. Introduction

Every year over 65,000 women are diagnosed with endometrial cancer (EC) in the US, and over 400,000 new cases are diagnosed worldwide [1,2]. While the rising incidence of endometrial cancer can be partially associated with the obesity epidemic and aging population,

* Corresponding author at: 1121 NW 14th St, Suite 345C, Miami, FL 33136, USA.
E-mail address: mschlumbrecht@miami.edu (M.P. Schlumbrecht).

https://doi.org/10.1016/j.ygyno.2023.07.008
0090-8258/

type II, or high-grade tumors, occur independent of estrogen-related risk factors and are associated with worse outcomes and survival. Despite rapid advances in cancer-directed therapies, EC has had the greatest increase in cancer related mortality among women [1,3]. Previous studies have demonstrated that EC is associated with one of the largest survival disparities, with Black women having higher rates of mortality than White women for every histologic subtype [1,4]. It has been hypothesized that these differences may be attributed to several factors including, but not limited to, advanced stage at the time of diagnosis, more aggressive histologies, limited access to care, and departure from guideline-concordant treatment among Black women [5–7]. To make this disparity more complex, other studies have shown that there may be intra-racial differences in EC survival outcomes [8,9]. Pinheiro et al. [9] determined that the overall survival of Black Hispanic women with EC was better than that of Caribbean-born Black women and US-born Black women. Similar results were found in a study of women with epithelial ovarian cancer, as Caribbean-born women of Hispanic ethnicity, regardless of race, had improved survival outcomes over non-Hispanic women [10]. These findings underscore the importance of further investigation into this under-studied population.

Due to forced migration from West Africa and various other societal factors, the genetic composition of the Black population in the Western Hemisphere is diverse [11]. The US Black population is comprised of both those born in US and those born in other countries who have immigrated to the US, a context which necessitates a more comprehensive and granular approach in making risk estimations [12]. In 2019, 46% of all Black immigrants to the US were born in Caribbean countries, with persons from Jamaica and Haiti contributing the most to the foreign-born Black population [13]. The genetic ancestry of those born in the Caribbean is distinct to each island and is heavily influenced by the island's geopolitical history. Hispaniola, the first island to be colonized in 1492, was eventually split into the Dominican Republic (Spain) and Haiti (France). Both countries experience extermination of Indigenous people and forced migration of West Africans. In 1804, the Haitian Afro-Caribbean population liberated the island, leading to Haiti's predominantly West African admixture (West African 99%; European 0.46%; <0.1% Indigenous) [14–16]. Great Britain colonized Jamaica in 1655. Jamaica had both slavery and indentured servitude until the late 1800s and experienced an influx of Europeans, Asians, and East Indians. This led to a more diverse genetic admixture (West African 82%, European 10%, Indigenous 6%, Asian/East Indian 2%) in Jamaicans. Similar to Jamaica, the US was colonized by Great Britain, impacted by forced migration of West Africans, and was faced with large waves of immigration from many different countries. The genetic admixture of US-born Black persons is also reflective of this history (West African 73%, European 24%, and Indigenous 1%) [15,16]. Combining this knowledge with the recent finding that increasing African ancestry is associated with serous EC suggests that there may be a gap in the understanding of women of African descent and endometrial cancer, as this group is typically studied altogether. Previous studies have demonstrated that Black immigrants in the US generally have better health outcomes; however, when looking specifically at cancer specific health outcomes the findings vary, especially regarding EC [8,17,18]. Factors including but not limited to acculturative stress, length of time spent in the US, presence of community or family support, and reason for leaving their home country have been shown to play a role in health outcomes of immigrants [18–21]. The rising incidence of EC in Black women necessitates a better understanding of these differences seen in survival in Black women as a whole and among the different subgroups of Black women.

There is limited knowledge of how specific country of birth is associated with EC outcomes. It is possible that country of birth may play a role in pathogenesis, as this factor may subject a woman to different socioenvironmental exposures, sociocultural practices, and molecular epigenetic changes. Prior research suggesting that women of Caribbean nativity have different risks than their US-born counterparts for aggressive, high grade endometrial pathologies, supports these hypotheses [8,22]. There are also data indicating that Caribbean-born Black women collectively may have an improved overall survival (OS) when compared to US-born Black women, but these populations have never been disaggregated by nativity to assess for variation in outcomes [8]. Geographic isolation of the Caribbean islands may increase the potential for less genetic diversity and augmentation of deleterious molecular signatures which increases cancer risk and affect treatment outcomes [23,24]. Given these previous findings, the objective of our study was to determine if country of birth influences overall survival in Black women with EC in the US, with an emphasis on those born in the US, Jamaica, and Haiti.

2. Materials and methods

2.1. Data sources

The Florida Cancer Data System (FCDS) is a statewide, comprehensive cancer surveillance system that has been collecting incidence data on all reportable cancer cases in Florida since 1981. FCDS is part of the Centers for Disease Control's National Program of Cancer Registries and meets national standards for completeness, timeliness, and data quality. These standards are followed by the North American Association of Central Cancer Registries (NAACCR). The study was completed under a state approved institutional review board (IRB) for coding and abstraction of the data. In March 2023, we used data from the FCDS to perform our analyses. Current guidelines at the time of data analysis used v.22 of the NAACR data dictionary.

2.2. Study cohort

We selected all cancer cases identified with the *International Classification of Diseases for Oncology*, 3rd edition, ICD-O-3 code C54.1 which incorporates "Corpus Uteri, Endometrium" cases diagnosed between January 1st, 1981 and December 31st, 2017 (latest available datapoints in FCDS to date). We included women that self-identified as Black and who were born in the US, Jamaica, or Haiti (USB: US-born Black woman, JBB: Jamaican-born Black woman, HBB: Haitian-born Black woman). Other Caribbean islands were excluded from analyses due to insufficient sample sizes. Cases of non-invasive cancer were also excluded.

2.3. Data collection

Captured variables included race, country of birth, age at diagnosis, date of diagnosis, date of death or last follow-up, vital status, stage of disease, type of insurance, tumor grade, tumor histology, lymphovascular space invasion (LVSI), tobacco use, date of receipt of chemotherapy, radiation therapy and/or surgery, and sequencing of systemic therapy and radiotherapy. Stage of disease was categorized as reported in FCDS following NAACCR guidelines: localized, regional, and distant (corresponding FIGO stages are in S1); type of insurance as private, Medicare only, Medicaid only, other insurance (which included having both Medicare and Medicaid) and No insurance. Tumor histology was classified following as described by Cote et al. [4] which characterized tumors as Clear cell (8310), Endometrioid (8050, 8140, 8143, 8210–8211, 8260–8263, 8340, 8380–8384, 8560, 8570), Mixed (8255, 8323), Malignant Mullerian mixed tumors (MMMT) and carcinosarcomas (8950–8951, 8980–8981), Serous (8441, 8460–8461) and Other (8000 8010 8013 8020 8021 8031 8041 8045 8070 8071 8072 8120 8245 8246 8440 8480 8481 8490 8574 8800 8801 8890 8891 8896 8900 8902 8910 8930 8931 8933 8935 8940 9071 9100 9105 9364 9473). Tumor histology and grade were combined to create two categories, low-grade endometrioid adenocarcinomas were considered Type I, and high-grade endometrioid adenocarcinomas, clear cell, serous, mixed cell and carcinosarcoma were categorized as Type II [25]. For the endometrioid histology only, tumor grades were grouped as

low grade (low and moderate differentiation) and high grade (poorly differentiated and anaplastic). Molecular subclassification of EC is not captured in the FCDS, so these data were not available for analysis. LVSI was binary (Yes/No). FCDS reports type of chemotherapy (single/multiple agents), radiation therapy and surgery, and these were used as a proxy to code for receipt of chemotherapy, radiation therapy or surgery respectively (Yes/No). Sequencing of systemic therapy and radiotherapy were used to categorize timing of Chemotherapy and Radiation as Adjuvant, Neoadjuvant, Intraoperatively, and Other. Type of surgery was classified as Hysterectomy, Other Surgery, Surgery NOS, and No Surgery. Further details regarding treatment modality (i.e., specific drug administered for chemotherapy) were not available. Tobacco use was classified as never or ever smoker. Overall survival (OS) was defined as time from date of diagnosis to all cause death or last follow-up in months corresponding to vital status (death/alive, respectively). Patients had follow-up censored at the date of last contact. A complete list of variables available in FCDS and all collapsed categories used in this study is available in Supplement S1.

2.4. Statistical analysis

All available data were included in the analyses, even when individual patient data was missing. Chi-square was used to assess associations between categorical variables and groups defined by country of birth. The analysis of variance (ANOVA) was used to assess differences in continuous variables among country of birth groups. OS was estimated by the Kaplan–Meier method. Comparison between survival curves by country of birth categories were assessed using the log-rank test for all tumor histologies grouped together and then further stratified by individual tumor histology category. The impact of missing values categories in OS was assessed in Supplement S2. Univariable and multivariable Cox proportional hazards regression analyses were performed to assess the effect of explanatory variables on OS. The multivariable model was adjusted for country of birth, age at diagnosis, type of insurance, stage of disease, tumor histology, LVSI, receipt of chemotherapy and receipt of surgery. Tumor grade was only considered in the univariable and multivariable analysis for endometrioid histology. Results were reported as hazard ratios (HR) with 95% confidence intervals (95% CI). All tests were two-sided, with statistical significance set at $p < 0.05$. Statistical analysis was performed using the SAS software 9.4 (SAS Institute Inc., Cary, NC) and R software 4.2.

3. Results

3.1. Patient characteristics

There were 79,913 EC cases diagnosed in Florida from 1981 through 2017. Fig. 1 demonstrates the application of our inclusion criteria. After applying our inclusion criteria, 3817 cases were available for analysis in this study.

Patient characteristics are summarized in Table 1. The average age at diagnosis was higher in JBB compared to USB and HBB (64.38 years vs 62.83 years vs 63.01 years respectively; $p = 0.0389$). USB more frequently had private insurance and a history of smoking compared to the other two groups ($p < 0.0001$). USB had a higher proportion of endometrioid cases compared to JBB (63.3% vs 52.3%, $p = 0.0028$) and HBB (63.3% vs 54.7%, $p = 0.0164$). Serous EC accounted for a larger proportion of JBB (14% vs 11.4%, $p = 0.0028$) and HBB cases (13.2 vs 11.4%, $p = 0.0164$) compared to USB. Additionally, the proportion of women with distant stage disease was significantly different (USB 16.4% vs JBB 19.5%, $p = 0.017$; USB 16.4% vs HBB 22.2%, $p = 0.002$). JBB had surgery performed as part of their treatment more often than USB (90.6% vs 83.5%, $p = 0.0002$) and HBB (90.6% vs 83.8%, $p = 0.004$), and the proportion of women who underwent a hysterectomy was significantly different between the three groups (USB vs JBB, $p < 0.0001$; USB vs HBB, $p = 0.001$; HBB vs JBB, $p = 0.112$). A smaller proportion of USB received chemotherapy compared to JBB ($p = 0.014$) and HBB ($p = 0.0003$).

3.2. Overall survival

HBB and USB had worse overall survival when evaluating all histologies together compared to JBB (Fig. 2A; median OS 35.7 months vs.

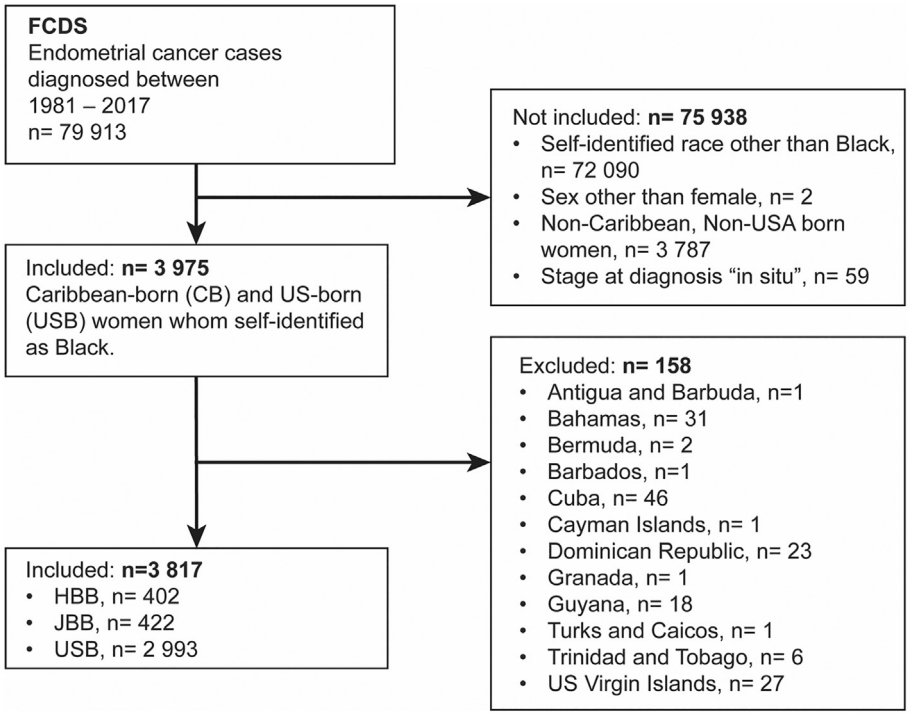

Fig. 1. Flowchart showing inclusion and exclusion criteria to select cases.

Table 1
Clinical and demographic characteristics of study cohort ($n = 3817$).

Variable	USB $n = 2993$	JBB $n = 422$	HBB $n = 402$	Entire Cohort n = 3817
Age in years, Mean (SD)	62.83 (12)	64.38 (11)	62.92 (10.74)	63.01 (11.78)
Insurance, (n,%)				
Private	848 (35.5)	120 (30.5)	105 (28.1)	1073 (34)
Medicaid	191 (8)	43 (10.9)	52 (13.9)	286 (9)
Medicare	707 (29.6)	102 (25.9)	97 (25.9)	906 (28.7)
Other insurance	466 (19.5)	57 (14.5)	57 (15.2)	580 (13.4)
No insurance	176 (7.3)	72 (18.3)	63 (16.8)	311 (9.9)
Unknown	605 (−)	28 (−)	28 (−)	661 (−)
Smoking Status, (n,%)				
Ever Smoker	553 (22.5)	36 (10)	33 (10)	662 (19.7)
Never Smoker	1910 (77.5)	323 (90)	299 (90)	2532 (80.3)
Unknown	530 (−)	63 (−)	70 (−)	663 (−)
Tumor Histology, (n,%)				
Endometrioid	1895 (63.3)	229 (52.3)	220 (54.7)	2344 (61.4)
Serous	342 (11.4)	59 (14)	53 (13.2)	454 (11.9)
Clear Cell	88 (2.9)	11 (2.6)	10 (2.5)	109 (2.9)
Carcinosarcoma	270 (9)	60 (14.2)	48 (11.9)	378 (9.9)
Mixed cells	116 (3.9)	18 (4.3)	23 (5.7)	157 (4.1)
Other histology	282 (9.4)	45 (10.7)	48 (13.2)	375 (9.8)
Stage, (n,%)				
Localized	1570 (56.6)	191 (49)	171 (47.5)	1932 (54.8)
Regional	749 (27)	123 (31.5)	109 (30.3)	981 (27.9)
Distant	454 (16.4)	76 (19.5)	80 (22.2)	610 (17.3)
Unstaged	220 (−)	32 (−)	42 (−)	294 (−)
Grade (Endometrioid only), (n,%)				
Low grade	1124 (67.7)	135 (68.5)	115 (67.3)	1374 (67.8)
High grade	536 (32.3)	62 (31.5)	56 (32.7)	654 (32.2)
Unknown	235 (−)	32 (−)	49 (−)	316 (−)
Tumor and Grade Histology, (n,%)				
Type I	1124 (45.4)	135 (39.1)	115 (37.7)	1374 (44)
Type II	1352 (54.6)	210 (60.9)	190 (62.3)	1752 (56)
LVSI, (n,%)				
Yes	316 (29.2)	50 (32.3)	51 (32.9)	417 (30)
No	765 (70.7)	105 (67.7)	104 (67.1)	974 (70)
Unknown	1912 (−)	267 (−)	247 (−)	2426 (−)
Surgery Performed, (n,%)				
Yes	2466 (83.5)	375 (90.6)	330 (83.8)	3171 (84.3)
No	487 (16.5)	39 (9.4)	64 (16.2)	590 (15.7)
Unknown	40 (−)	8 (−)	8 (−)	56 (−)
Radiation Therapy, (n,%)				
Yes	754 (25.8)	98 (24)	85 (21.7)	2786 (74.8)
No	2169 (74.2)	310 (76)	307 (78.3)	937 (25.2)
Unknown	70 (−)	14 (−)	10 (−)	94 (−)
Chemotherapy, (n,%)				
Yes	683 (23.6)	118 (29.3)	124 (32)	925 (25.1)
No	2206 (76.4)	285 (70.7)	262 (68)	2753 (74.9)
Unknown	104 (−)	19 (−)	16 (−)	139 (−)
Type of Surgery, (n,%)				
No surgery	504 (17)	43 (10.2)	69 (17.2)	616 (16.2)
Hysterectomy	2034 (68.4)	354 (84.3)	301 (75.1)	2689 (70.9)
Other surgery	71 (2.4)	7 (1.7)	10 (2.5)	88 (2.3)
Surgery, NOS	363 (12.2)	16 (3.8)	21 (5.2)	400 (10.6)
Unknown	21 (−)	2 (−)	1 (−)	24 (−)

* LVSI- Lymphovascular space invasion, NOS: Not otherwise specified.

43.3 months vs. 56 months respectively, $p = 0.0061$). This difference in OS was also found specifically in women with serous EC (Fig. 2C; OS 18.5 months HBB, 29.9 months USB, 41.0 months JBB, $p = 0.013$). There was no difference in OS by nativity in women with endometrioid and carcinosarcoma histologies (Fig. 2B and D). Kaplan-Meier curves were created to evaluate potential confounders in the unknown observations and demonstrated equal distribution among the categories of interest. (Supplement S2).

The results from the univariable Cox regression analysis for OS are shown in Table 2 and Supplement S3. For all histologies, HBB had worse OS compared to USB (hazard ratio [HR] 1.22, 95% confidence interval [CI]: 1.06–1.40). Additionally, HBB with serous EC experienced lower OS when compared to USB (HR 1.53, 95% CI: 1.05–2.21). A statistically significant difference in OS was not observed in JBB compared to USB with serous EC (HR 0.75, 95% CI: 0.53–1.06, $p = 0.108$). There was also no statistically significant difference in OS based on country of birth for endometrioid and carcinosarcoma.

The multivariable Cox regression model for OS is shown in Table 3. After controlling for potential confounders in this model, for all histologies, HBB remained a significant predictor of OS when compared to USB (HR 1.54, 95% CI: 1.18–2.00, $p = 0.001$) and JBB (HR 1.77 95% CI: 1.25–2.53, p = 0.001). When stratified by histology types, among women with endometrioid histology, there was a significant difference in JBB compared to USB (HR 1.66, 95% CI: 1.07–2.60, $p = 0.025$) and HBB compared to USB (HR 1.77 HR 95% CI: 1.10–2.83, $p = 0.018$). There was no difference in OS for country of birth in the serous and carcinosarcoma models. Positive predictors of OS were receipt of chemotherapy (for all histologies together, serous EC, and carcinosarcoma) and receipt of surgery (for all histologies together, endometrioid EC, and carcinosarcoma). Negative

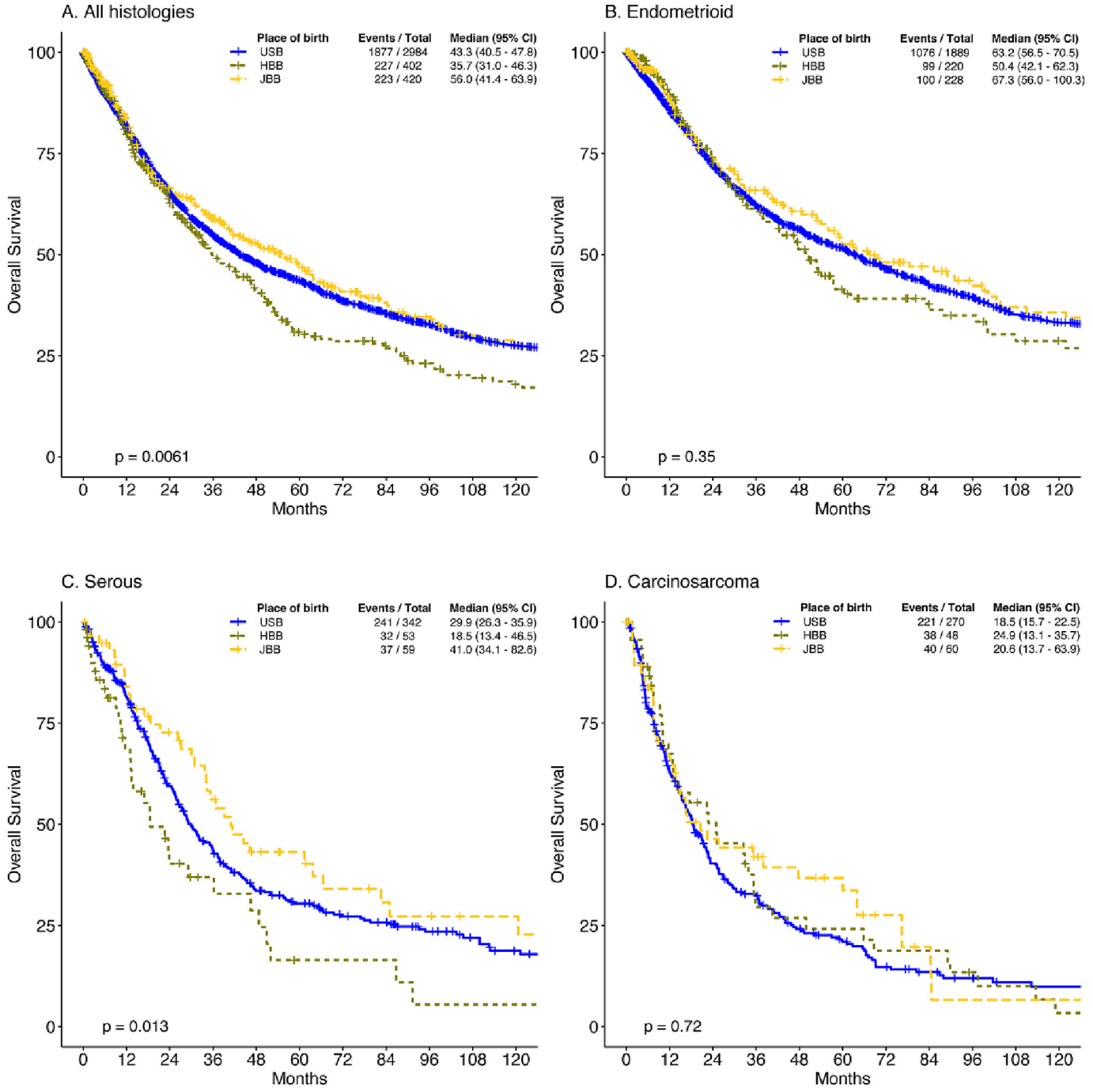

Fig. 2. Overall survival by place of birth in all histologies (A), and in Endometrioid (B), Serous (C) and Carcinosarcoma (D) histologies.

Table 2
Univariable Cox regression for overall survival.

Variable	All Histologies		Endometrioid		Serous		Carcinosarcoma	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Country of birth								
US	Ref		Ref		Ref		Ref	
Jamaica	0.92 (0.80–1.06)	0.269	0.89 (0.73–1.10)	0.281	0.75 (0.53–1.06)	0.108	0.93 (0.66–1.32)	0.693
Haiti	**1.22 (1.06–1.40)**	**0.004**	1.10 (0.89–1.35)	0.386	**1.53 (1.05–2.21)**	**0.025**	0.88 (0.62–1.23)	0.448

Table 3
Multivariable Cox regression for overall survival.

Variable	All Histologies (555 events in $n = 1310$)		Endometrioid (205 events in $n = 669$)		Serous (122 events in $n = 208$)		Carcino-sarcoma (96 events in $n = 138$)	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age, 1-year increase	**1.03 (1.02–1.05)**	**<0.001**	**1.04 (1.02–1.06)**	**<0.001**	1.02 (0.99–1.06)	0.13	**1.01 (0.98–1.05)**	**0.04**
Insurance								
Private	Ref		Ref		Ref		Ref	
Medicaid	1.35 (0.97–1.90)	0.078	1.26 (0.68–2.34)	0.455	0.71 (0.34–1.51)	0.374	2.15 (0.88–5.23)	0.092
Medicare	0.99 (0.78–1.25)	0.930	0.97 (0.65–1.45)	0.892	1.02 (0.62–1.70)	0.931	1.73 (0.88–3.39)	0.11
Other insurance	1.03 (078–1.37)	0.831	1.19 (0.77–1.85)	0.428	0.64 (0.33–1.24)	0.186	1.61 (0.68–3.84)	0.282
No insurance	1.19 (0.85–1.66)	0.314	1.50 (0.85–2.68)	0.165	1.57 (0.71–3.47)	0.265	0.93 (0.39–2.25)	0.878
Stage								
Localized	Ref		Ref		Ref		Ref	
Regional	**1.52 (1.22–1.89)**	**<0.001**	1.12 (0.78–1.60)	0.542	**2.84 (1.66–4.87)**	**<0.001**	0.90 (0.48–1.67)	0.728
Distant	**3.73 (2.84–4.89)**	**<0.001**	**2.82 (1.74–4.58)**	**<0.001**	**5.47 (3.03–9.86)**	**<0.001**	**2.19 (1.19–4.03)**	**0.012**
Grade								
Low Grade	–		Ref		–		–	
High Grade	–	–	**2.04 (1.48–2.80)**	**<0.001**	–	–	–	–
LVSI								
No	Ref		Ref		Ref		Ref	
Yes	**1.96 (1.61–2.39)**	**<0.001**	**2.57 (1.82–3.61)**	**<0.001**	**2.07 (1.38–3.12)**	**<0.001**	**2.30 (1.41–3.74)**	**<0.001**
Chemo-therapy								
No	Ref		Ref		Ref		Ref	
Yes	**0.77 (0.62–0.95)**	**0.014**	0.87 (0.6–1.26)	0.452	**0.46 (0.30–0.71)**	**<0.001**	**0.52 (0.33–0.84)**	**0.007**
Surgery								
No	Ref		Ref		Ref		Ref	
Yes	**0.47 (0.29–0.75)**	**0.002**	**0.11 (0.05–0.25)**	**<0.001**	1.15 (0.34–3.90)	0.82	**0.12 (0.03–0.41)**	**<0.001**
Country of birth								
US	Ref		Ref		Ref		Ref	
Jamaica	0.87 (0.66–1.15)	0.317	**1.66 (1.07–2.60)**	**0.025**	0.88 (0.44–1.75)	0.108	0.48 (0.21–1.10)	0.083
Haiti	**1.54 (1.18–2.00)**	**0.001**	**1.77 (1.10–2.83)**	**0.018**	1.79 (0.94–3.42)	0.078	1.29 (0.66–2.50)	0.454
Histology								
Endometrioid	Ref		–	–	–	–	–	–
Serous	1.14 (0.89–1.45)	0.303	–	–	–	–	–	–
Carcino-sarcoma	**1.72 (1.32–2.24)**	**<0.001**	–	–	–	–	–	–
Clear cell	1.08 (0.67–1.72)	0.756	–	–	–	–	–	–
Mixed cell	1.34 (0.99–1.83)	0.062	–	–	–	–	–	–
Other	**2.40 (1.63–3.54)**	**<0.001**	–	–	–	–	–	–

*LVSI- Lymphovascular space invasion.

predictors of OS were distant stage, high grade (for endometrioid histology only), and lymphovascular space invasion).

4. Discussion

Black women experience worse outcomes across all stages and histologies of EC [1,3,4]. This is one of the first studies exploring the differences in EC outcomes based on country of birth in Black women. Given the high number of Caribbean immigrants in Florida, we were able to disaggregate our Black population by country of birth and evaluate if this is associated with survival outcomes for Black women. In this cohort, we found that HBB women experienced worse OS than UBB when looking at all histologies together, and when evaluating only serous EC, HBB women experienced a significantly decreased OS compared to UBB. This may be explained by the fact that over 50% of HBB were diagnosed with regional or distant stage EC, and it is well known that stage is an important predictor of overall survival in EC [26]. There was no statistically significant survival difference in HBB with serous EC compared to USB on multivariable analysis. Additionally, country of birth was not significant on univariable analysis for women with endometrioid EC, however on multivariable analysis, country of birth became a statistically significant predictor of worse overall survival in JBB and HBB with endometrioid EC compared to USB. Because all-cause mortality is used in this analysis, these data suggest that other medical co-morbidities and social factors unaccounted for in the database may contribute to the mortality risk seen in women with endometrioid EC. The findings of this study provide additional insight into the intra-racial differences of Black women with EC, consistent with the findings in prior studies [9,10]. These studies suggest that country of birth in addition to race and ethnicity predict survival outcomes of women diagnosed with EC, underscoring the importance of personalized risk stratification in this context.

It is important to explore the social factors that may help explain the difference in outcomes seen HBB compared to USB. Saint-Jean et al. [27] described the effect that the "triple minority status" has on Haitian immigrants as they must overcome being Black, Haitian Creole-speaking foreigners. The effect that language barriers and English proficiency have on access to care, clinical trial enrollment, and health outcomes is well studied [28–32]. Recently, Roy et al. [29] identified in a cohort of cervical cancer patients that Black women and Haitian Creole speaking women had a prolonged time to treatment initiation. It is also well described in the literature that prolonged time to treatment initiation can lead to increased mortality, and Black women are more likely to have treatment delays [33,34]. USB and JBB may have an inherent survival advantage over HBB due to the lack of language barriers when seeking medical care. Although JBB do not experience significant language barriers in the US, there are other components that may lead to acculturative stress or lack thereof which ultimately affects health outcomes including differences in culture, socioeconomic status, perception of health care, and family or community support [19–21]. Another potential delay in care that may contribute to the differences in stage at presentation and outcomes is the timing of immigration to the US, as some women may have traveled to the US with intentions of seeking medical care for their malignancy. In these instances, a woman may experience difficulty in establishing care if uninsured or underinsured or are lacking social support. Also, if a woman were to have traveled to the US for treatment of their malignancy, the data on the interval of time between diagnosis in another country and treatment in the US was not available, and this could play a role in the disparities of stage at presentation. Due to the limitations of the FCDS

database, we were unable to evaluate these factors, but they are ones to be considered in future studies.

Treatment patterns varied between the three groups in this study. The proportion of JBB that had surgery performed as part of their treatment was highest among the three groups, despite having a lower proportion of localized disease. Additionally, JBB had a higher proportion of women receiving chemotherapy for treatment compared to USB. These findings suggest that JBB may be more accepting of surgical management than their Haitian-born and US-born counterparts. We must also consider how the language barrier of HBB plays a role in the results, as there may be apprehension to accept surgery if risks, benefits, and alternatives are inadequately explained to them. Due to the limitations of our data, we are unable to determine how often surgery was offered and subsequently refused or what factors led to a woman's decision to undergo surgery. Prospective studies to understand and address the sociocultural factors contributing to this difference in treatment may help to improve receipt of guideline based treatment and survival outcomes.

The Trans-Atlantic slave trade and geopolitics have made a significant impact on the genetic admixture currently seen in the Black population living in the Americas. There are known variations in the degree of contribution of African ancestry in the countries of interest for this study which may play a role in the results found. More specifically, there has been a larger percentage of African ancestry identified in the Haitian population compared to those born in the US or Jamaica [14–16]. The difference in survival of HBB with serous EC living in the US compared to the other groups may be a consequence of this as it has also been previously identified that increasing African ancestry is associated with serous EC [35].

The landscape of EC classification and therapy is evolving rapidly with the identification of distinct molecular and genetic footprints. The intra-racial differences in outcomes reported in this study suggest that there is an interplay between social factors and genetic and molecular characteristics. Data from The Cancer Genome Atlas (TCGA) analyzed by Dubil et al. [36] found that compared to White women, Black women were more likely to have tumors that were copy number variant (CNV) high, of mitotic subtype, or had extensive somatic copy number alterations (SCNAs), all of which are associated with more aggressive phenotype [36,37]. Sanchez-Covarrubias et al. [35] also noted that increasing African ancestry was associated with increasing odds of CNV high tumors. When considering the heterogeneity of Black women, the survival disparities recognized in our study, and these known molecular subtypes and genetic associations, the effect that molecular differences have on disparities in women with EC becomes more plausible. This study was limited to the histologic classification of EC, and it does not account for the paradigm shift in characterization of EC with molecular sub-classifications as determined by TCGA Research Network [37]. The findings of this study should direct future studies to investigate how survival outcomes are impacted by country of birth when accounting for differences in molecular sub-classification.

JBB and HBB had a higher percentage of women with Type II EC compared to USB secondary to the higher percentage of serous and carcinosarcoma histologies in these two groups. These rates of Type II EC seen in the JBB and HBB are also higher than what has been described in literature for African American women [38]. This emphasizes the notion that the Caribbean born population residing in the US may be a particularly vulnerable population with regards to EC and encourages additional exploration to better define these disparities especially in comparison to those who remain in their native countries.

There are several limitations to our study that should be considered. First, our analysis was limited by the variables collected for the cancer registry. While the FCDS provided access to a large volume of standardized data, information like primary language spoken, interval of time between diagnosis and primary treatment, and cause of death were unavailable. These factors may have provided more knowledge about the disparities than were identified. Another factor to consider is that all-cause mortality was used for the survival analysis, because cancer-specific mortality was not available for this dataset. Thus, other medical co-morbidities may be contributing to the risk for death, especially for women with endometrioid EC. Also, the data collection for this study spans over thirty-five years. There may be a temporal bias in play as there have been changes over time in how EC is treated including chemotherapy and immunotherapy regimens and surgical approaches. Additionally, the changing socio-political climates in the Caribbean countries during this time period may have impacted immigration patterns and the distribution of these women in our cohort. However, in the interest in accumulating a sufficient cohort, we opted to include all years represented in the database. Another weakness of our study is that due to low counts of women from other countries, only Black women born in the US, Jamaica, and Haiti were included. Women from other immigrant groups, underrepresented in this dataset, may have further differences than what is seen in the groups that were analyzed. Therefore, future investigation of Black women born in other countries is warranted. Additionally, although this is one of the first studies to evaluate intra-racial differences of Black women with EC, the outcomes determined from the Black population in Florida may not be generalizable to the rest of the country due to its large immigrant population. However, Florida is uniquely positioned geographically to be able to study these groups of people since it is a major port of entry for Caribbean immigrants. Florida is also not in the Surveillance, Epidemiology, and End Results (SEER) Program and thus, using the FCDS database has allowed for investigation into heterogeneity of the Black population in the US which may otherwise be unaccounted for. Despite these limitations, this study contributes to our current understanding of racial disparities associated with EC and provides justification for further research in this field.

5. Conclusion

This study calls attention to the notion that Black women with EC are not all the same and strengthens the developing body of work focused on health disparities. Race unifies this group of people in way that describes a risk of vulnerability to racism and social oppression in the US, for both Black individuals native to the US and Black immigrants. Categorizing individuals by this social construct creates a blind spot when used to describe and compare the variations in health outcomes. Although the extent of the differences has not yet been established, there may be subgroups of women diagnosed with EC which may require modifications to treatment and surveillance based on characteristics other than race as an identifying characteristic. Future research combining clinical, genetic, and molecular data while overlaying the important sociocultural and geographic contexts of women who identify as the same race will help to explain disparities more precisely and guide treatment recommendations in this vulnerable population.

CRediT authorship contribution statement

Alyssa J. Mercadel: Investigation, Writing – original draft, Writing – review & editing. **Alex P. Sanchez-Covarrubias:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Heidy N. Medina:** Writing – review & editing. **Paulo S. Pinheiro:** Writing – review & editing. **Andre Pinto:** Writing – review & editing. **Sophia H.L. George:** Writing – review & editing, Supervision. **Matthew P. Schlumbrecht:** Conceptualization, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors have no conflicts of interest or funding to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.07.008.

References

[1] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, CA Cancer J. Clin. 73 (1) (2023) 17–48, https://doi.org/10.3322/caac.21763 (PubMed PMID: 36633525).

[2] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249, Epub 20210204, https://doi.org/10.3322/caac.21660 PubMed PMID: 33538338.

[3] S.J. Henley, J.W. Miller, N.F. Dowling, V.B. Benard, L.C. Richardson, Uterine Cancer Incidence and Mortality - United States, 1999–2016, MMWR Morb. Mortal. Wkly Rep. 67 (48) (2018), https://doi.org/10.15585/mmwr.mm6748a1 1333–8. Epub 20181207. PubMed PMID: 30521505; PMCID: PMC6329484.

[4] M.L. Cote, J.J. Ruterbusch, S.H. Olson, K. Lu, R. Ali-Fehmi, The growing burden of endometrial cancer: a major racial disparity affecting black women, Cancer Epidemiol. Biomark. Prev. 24 (9) (2015) 1407–1415, Epub 20150819, https://doi.org/10.1158/1055-9965.EPI-15-0316 PubMed PMID: 26290568.

[5] M. Kaspers, E. Llamocca, A. Quick, J. Dholakia, R. Salani, A.S. Felix, Black and Hispanic women are less likely than white women to receive guideline-concordant endometrial cancer treatment, Am. J. Obstet. Gynecol. 223 (3) (2020), https://doi.org/10.1016/j.ajog.2020.02.041 398 e1- e18. Epub 20200303. PubMed PMID: 32142825; PMCID: PMC7483220.

[6] S. Sud, J. Holmes, M. Eblan, R. Chen, E. Jones, Clinical characteristics associated with racial disparities in endometrial cancer outcomes: A surveillance, epidemiology and end results analysis, Gynecol. Oncol. 148 (2) (2018) 349–356, Epub 20171221, https://doi.org/10.1016/j.ygyno.2017.12.021 PubMed PMID: 29276059.

[7] K.M. Doll, B. Hempstead, J. Alson, L. Sage, D. Lavallee, Assessment of Prediagnostic experiences of black women with endometrial cancer in the United States, JAMA Netw. Open 3 (5) (2020), https://doi.org/10.1001/jamanetworkopen.2020.4954 e204954. Epub 20200501. (PubMed PMID: 32412636; PMCID: PMC7229523).

[8] M. Schlumbrecht, M. Huang, J. Hurley, S. George, Endometrial cancer outcomes among non-Hispanic US born and Caribbean born black women, Int. J. Gynecol. Cancer (2019), https://doi.org/10.1136/ijgc-2019-000347 Epub 20190503. PubMed PMID: 31055453; PMCID: PMC7039733.

[9] P.S. Pinheiro, H.N. Medina, T. Koru-Sengul, B. Qiao, M. Schymura, E.N. Kobetz, M.P. Schlumbrecht, Endometrial cancer type 2 incidence and survival disparities within subsets of the US Black Population, Front. Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.699577 699577. Epub 20210720. PubMed PMID: 34354948; PMCID: PMC8329656.

[10] M. Schlumbrecht, D. Cerbon, M. Castillo, S. Jordan, R. Butler, A. Pinto, S. George, Race and ethnicity influence survival outcomes in women of caribbean nativity with epithelial ovarian cancer, Front. Oncol. 10 (2020) 880, Epub 20200529, https://doi.org/10.3389/fonc.2020.00880 PubMed PMID: 32547957; PMCID: PMC7273510.

[11] S. Baharian, M. Barakatt, C.R. Gignoux, S. Shringarpure, J. Errington, W.J. Blot, C.D. Bustamante, E.E. Kenny, S.M. Williams, M.C. Aldrich, S. Gravel, The great migration and African-American genomic diversity, PLoS Genet. 12 (5) (2016), https://doi.org/10.1371/journal.pgen.1006059 e1006059. Epub 20160527. (PubMed PMID: 27232753; PMCID: PMC4883799).

[12] C.M. Arthur, E.S. Katkin, Making a case for the examination of ethnicity of blacks in United States Health Research, J. Health Care Poor Underserved 17 (1) (2006) 25–36, https://doi.org/10.1353/hpu.2006.0017 (PubMed PMID: 16520504).

[13] C. Tamir, The Growing Diversity of Black America Pew Research Center, [cited 2023 January 18]. Available from: https://www.pewresearch.org/social-trends/wp-content/uploads/sites/3/2021/03/RE_2021.03.25_Black-Americans_FINAL.pdf 2021.

[14] A.G. Sepinwall, A.G. Sepinwall, ProQuest, Haitian History: New Perspectives, Routledge, New York, 2013.

[15] K. Adhikari, J.C. Chacón-Duque, J. Mendoza-Revilla, M. Fuentes-Guajardo, A. Ruiz-Linares, The genetic diversity of the Americas, Annu. Rev. Genomics Hum. Genet. 18 (1) (2017) 277–296, https://doi.org/10.1146/annurev-genom-083115-022331 (PubMed PMID: 28859572).

[16] J.L. Wilson, V. Saint-Louis, J.O. Auguste, B.A. Jackson, Forensic analysis of mtDNA haplotypes from two rural communities in Haiti reflects their population history, J. Forensic Sci. 57 (6) (2012) 1457–1466, Epub 20120514, https://doi.org/10.1111/j.1556-4029.2012.02186.x PubMed PMID: 22583388.

[17] P.S. Pinheiro, K.E. Callahan, C. Ragin, R.W. Hage, T. Hylton, E.N. Kobetz, Black heterogeneity in cancer mortality: US-blacks, Haitians, and Jamaicans, Cancer Control 23 (4) (2016) 347–358, https://doi.org/10.1177/107327481602300406. PubMed PMID: 27842324; PMCID: PMC5321133.

[18] M.A. Ifatunji, Y. Faustin, W. Lee, D. Wallace, Black nativity and health disparities: a research paradigm for understanding the social determinants of health, Int. J. Environ. Res. Public Health 19 (15) (2022), https://doi.org/10.3390/ijerph19159166 Epub 20220727. PubMed PMID: 35954520; PMCID: PMC9367942.

[19] D. Fanfan, C.S. Rodriguez, M. Groer, M. Weaver, J.R. Stacciarini, Stress and depression in the context of migration among Haitians in the United States, Health Soc. Care Community 28 (5) (2020) 1795–1806, Epub 20200423, https://doi.org/10.1111/hsc.13006 PubMed PMID: 32323900.

[20] C.L. Erving, Stress exposure and physical health among Older African American and Caribbean Black women, J. Aging Health 34 (3) (2022) 320–333, Epub 20220412, https://doi.org/10.1177/08982643221085406 PubMed PMID: 35411820; PMCID: PMC9133181.

[21] I.L. Livingston, M. Neita, L. Riviere, S.L. Livingston, Gender, acculturative stress and Caribbean immigrants' health in the United States of America: an exploratory study, West Indian Med. J. 56 (3) (2007) 213–222, https://doi.org/10.1590/s0043-31442007000300004 (PubMed PMID: 18072399).

[22] A. Creque, E. Taioli, A. Attong-Rogers, C. Ragin, Disparities in uterine cancer survival in a Brooklyn cohort of black women, Future Oncol. 6 (2) (2010) 319–327, https://doi.org/10.2217/fon.09.169 (PubMed PMID: 20146590).

[23] M. Arcos-Burgos, M. Muenke, Genetics of population isolates, Clin. Genet. 61 (4) (2002) 233–247, https://doi.org/10.1034/j.1399-0004.2002.610401.x (PubMed PMID: 12030885).

[24] K. Hatzikotoulas, A. Gilly, E. Zeggini, Using population isolates in genetic association studies, Brief Funct. Genomics 13 (5) (2014) 371–377, Epub 20140709, https://doi.org/10.1093/bfgp/elu022 PubMed PMID: 25009120; PMCID: PMC4168662.

[25] W.T. Creasman, S. Ali, D.G. Mutch, R.J. Zaino, M.A. Powell, R.S. Mannel, F.J. Backes, P.A. DiSilvestro, P.A. Argenta, M.L. Pearl, S.B. Lele, S.R. Guntupalli, S. Waggoner, N. Spirtos, J.F. Boggess, R.P. Edwards, V.L. Filiaci, D.S. Miller, Surgical-pathological findings in type 1 and 2 endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study on GOG-210 protocol, Gynecol. Oncol. 145 (3) (2017) 519–525, Epub 20170406, https://doi.org/10.1016/j.ygyno.2017.03.017 PubMed PMID: 28392124; PMCID: PMC5702929.

[26] S.N. Lewin, T.J. Herzog, N.I. Barrena Medel, I. Deutsch, W.M. Burke, X. Sun, J.D. Wright, Comparative performance of the 2009 international federation of gynecology and obstetrics' staging system for uterine corpus cancer, Obstet. Gynecol. 116 (5) (2010) 1141–1149, https://doi.org/10.1097/AOG.0b013e3181f39849 (PubMed PMID: 20966700).

[27] G. Saint-Jean, L.A. Crandall, Sources and barriers to health care coverage for Haitian immigrants in Miami-Dade county, Florida, J. Health Care Poor Underserved 16 (1) (2005) 29–41, https://doi.org/10.1353/hpu.2005.0016 (PubMed PMID: 15741707).

[28] S. Jorge, S. Masshoor, H.J. Gray, E.M. Swisher, K.M. Doll, Participation of patients with limited english proficiency in gynecologic oncology clinical trials, J. Natl. Compr. Cancer Netw. 21 (1) (2023) 27–32 e2, https://doi.org/10.6004/jnccn.2022.7068 (PubMed PMID: 36634612).

[29] M. Roy, L. Finch, D. Kwon, S.E. Jordan, S. Yadegarynia, A.H. Wolfson, B. Slomovitz, L. Portelance, M. Huang, Factors contributing to delays in initiation of front-line cervical cancer therapy: disparities in a diverse south Florida population, Int. J. Gynecol. Cancer 32 (11) (2022) 1387–1394, Epub 20221107, https://doi.org/10.1136/ijgc-2022-003475 PubMed PMID: 36198435; PMCID: PMC9664089.

[30] R. Gulati, K. Hur, Association between limited English proficiency and healthcare access and utilization in California, J. Immigr. Minor. Health 24 (2022) 95–101.

[31] A.M. Foiles Sifuentes, M. Robledo Cornejo, N.C. Li, M.A. Castaneda-Avila, J. Tjia, K.L. Lapane, The role of limited english proficiency and access to health insurance and health care in the affordable care act era, Health Equity 4 (1) (2020) 509–517, Epub 20201211, https://doi.org/10.1089/heq.2020.0057 PubMed PMID: 33376934; PMCID: PMC7757700.

[32] M. Roy, N. Purington, M. Liu, D.W. Blayney, A.W. Kurian, L. Schapira, Limited English proficiency and disparities in health care engagement among patients with breast cancer, JCO Oncol. Pract. 17 (12) (2021), https://doi.org/10.1200/op.20.01093 e1837-e45. Epub 20210412. PubMed PMID: 33844591; PMCID: PMC9810131.

[33] D. Dolly, A. Mihai, B.J. Rimel, L. Fogg, J. Rotmensch, A. Guirguis, E. Yordan, S. Dewdney, A delay from diagnosis to treatment is associated with a decreased overall survival for patients with endometrial cancer, Front. Oncol. 6 (2016) 31, Epub 20160212, https://doi.org/10.3389/fonc.2016.00031 PubMed PMID: 26904507; PMCID: PMC4751250.

[34] A.E. Strohl, J.M. Feinglass, S. Shahabi, M.A. Simon, Surgical wait time: A new health indicator in women with endometrial cancer, Gynecol. Oncol. 141 (3) (2016) 511–515, Epub 20160423, https://doi.org/10.1016/j.ygyno.2016.04.014 PubMed PMID: 27103178; PMCID: PMC5989709.

[35] A.P. Sanchez-Covarrubias, A.D. Tabuyo-Martin, S. George, M. Schlumbrecht, African ancestry is associated with aggressive endometrial cancer, Am. J. Obstet. Gynecol. 228 (1) (2023), https://doi.org/10.1016/j.ajog.2022.07.040 92–5 e10. Epub 20220806. PubMed PMID: 35944605.

[36] E.A. Dubil, C. Tian, G. Wang, C.M. Tarney, N.W. Bateman, D.A. Levine, T.P. Conrads, C.A. Hamilton, G.L. Maxwell, K.M. Darcy, Racial disparities in molecular subtypes of endometrial cancer, Gynecol. Oncol. 149 (1) (2018) 106–116, https://doi.org/10.1016/j.ygyno.2017.12.009.

[37] Cancer Genome Atlas Research N, C. Kandoth, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, H. Shen, A.G. Robertson, I. Pashtan, R. Shen, C.C. Benz, C. Yau, P.W. Laird, L. Ding, W. Zhang, G.B. Mills, R. Kucherlapati, E.R. Mardis, D.A. Levine, Integrated genomic characterization of endometrial carcinoma, Nature. 497 (7447) (2013) 67–73, https://doi.org/10.1038/nature12113 (PubMed PMID: 23636398; PMCID: PMC3704730).

[38] Z.D. Horne, S.R. Teterichko, S.M. Glaser, R.E. Wegner, S. Hasan, S.M. Crafton, E.M. Miller, T.C. Krivak, A. Viswanathan, A.B. Olawaiye, P. Sukumvanich, S. Beriwal, Race-driven survival differential in women diagnosed with endometrial cancers in the USA, Int. J. Gynecol. Cancer 30 (12) (2020) 1893–1901, Epub 20200825, https://doi.org/10.1136/ijgc-2020-001560 PubMed PMID: 32847996.