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The impact of race, comorbid conditions and obesity on survival endpoints in women with high grade endometrial carcinoma

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HIGHLIGHTS

- Race and body mass index interact in high grade endometrial carcinoma survival.
- Comorbidities negatively impact high grade endometrial cancer survival.
- Guideline-concordant treatment decreases hazard of endometrial carcinoma death.

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ABSTRACT

Objective. To estimate overall survival, disease-specific survival, and progression-free survival among high grade endometrial carcinoma cases and to determine factors impacting survival for non-Hispanic white and non-Hispanic black women.

Methods. We identified high grade endometrial carcinoma cases among non-Hispanic white and non-Hispanic black women from ongoing institutional studies, and determined eligibility through medical record and pathologic review. We estimated effects of demographic and clinical variables on survival outcomes using Kaplan Meier methods and Cox proportional hazards modelling.

Results. Non-Hispanic Black women with BMI <25.0 had poorest overall survival compared to non-Hispanic white women with BMI <25.0 (HR 3.03; 95% CI [1.35, 6.81]), followed by non-Hispanic black women with BMI 25.0+ (HR 2.43; 95% CI [1.28, 4.60]). A similar pattern emerged for disease-specific survival. Non-Hispanic black women also had poorer progression-free survival than non-Hispanic white women (HR 1.40; 95% CI [1.01, 1.93]). Other significant factors impacting survival outcomes included receipt of National Cancer Center Network (NCCN) guideline-concordant treatment (GCT), earlier stage at diagnosis, and fewer comorbid conditions.

Conclusions. BMI and race interact and modify the association with high grade endometrial carcinoma survival. Other potentially modifiable factors, such as reducing comorbidities and increasing access to GCT will potentially improve survival after diagnosis of high grade endometrial carcinomas. A better understanding of the molecular drivers of these high grade carcinomas may lead to targeted therapies that reduce morbidity and mortality associated with these aggressive tumors.

1. Introduction

Endometrial carcinoma is the most common gynecological cancer in the United States, and the American Cancer Society estimates that there were approximately 65,600 new cases of endometrial cancer in the US in 2020 [1]. Incidence rates of endometrial cancer have been rising for decades, from 23.7 per 100,000 in 2000 to 27.2 per 100,000 in 2017, and are projected to continue rising [2,3]. Incidence rates were previously thought to be highest among non-Hispanic white (NHW) women; however, once corrected for hysterectomy status, incidence rates of endometrial cancer are substantially higher among non-Hispanic black (NHB) women [4,5]. From 2012 to 2014, hysterectomy-corrected incidence rates of endometrial cancer were estimated at 102

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per 100,000 NHB women, compared to 86 per 100,000 NHW women [4]. Endometrial carcinoma also has one of the highest survival disparities in cancer, with consistent estimates over the last several decades reporting that NHB women are 80% more likely to die from this disease compared to NHW women [5,6].

Among endometrial carcinomas, the low grade endometrioid histologic subtype is the least aggressive and most common [7]. Rates of this subtype remained mostly stable for NHW women from 2000 to 2015, while rates of endometrioid subtype in racial and ethnic minorities, and rates of non-endometrioid subtypes for all women, increased substantially [8]. Non-endometrioid histologic subtypes, such as clear cell, serous, and carcinosarcoma, are usually classified as high grade, are more commonly diagnosed in NHB women, and have worse outcomes and survival [8,9]. Among endometrial cancer cases registered by the Surveillance, Epidemiology, and End Results (SEER) program from 2000 to 2011, 36% of NHB cancers were high grade, compared to 21% of NHW cases [10]. While NHB women are more likely to be diagnosed with these more aggressive subtypes [11], it doesn"t entirely account for the survival disparity [10]. Literature exploring the endometrial cancer survival disparity often considers race only a biological construct, rather than as a proxy for modifiable contributors to racial disparities, such as treatment inequity and the importance of early diagnosis [12].

Many epidemiologic studies of endometrial cancer do not have adequate numbers of non-white women [5], and many studies combine high and low grade cancers. Thus, most of our knowledge surrounding endometrial cancer incidence and survival from an epidemiologic perspective is based on low grade, endometrioid tumors in NHW women. As high grade tumors are more aggressive, and result in the greatest morbidity and mortality from this disease, research specifically focused on these endometrial cancer types is needed. Here, we estimated overall survival, disease-specific survival, and progression free survival, including clinical and demographic factors that may impact survival after a diagnosis of high grade endometrial carcinoma in NHB and NHW women from two large, urban medical centers. We hypothesized that after adjustment for individual-level variables, the higher risks of death among NHB women with high grade endometrial carcinomas seen in population-based studies would be attenuated.

2. Methods

2.1. Case identification

Potential cases were identified from ongoing observational studies (housed in radiation oncology at Henry Ford Health System and pathology at Karmanos Cancer Institute), and supplemented with data from the Metropolitan Detroit Cancer Surveillance System (MDCSS). The MDCSS has continuously provided active identification and follow up of malignant tumors diagnosed in all residents of Wayne, Macomb, and Oakland counties of Michigan since 1973 as one of the founding registries in the Surveillance, Epidemiology and End Results program. Here, eligible cases included NHB and NHW women, ages 21–79 at diagnosis, diagnosed with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I-III, and received a hysterectomy at Henry Ford Health System (HFHS) or Karmanos Cancer Institute (KCI) with or without adjuvant therapies. Grade and histological subtype were reviewed by a gynecologic pathologist (RAF). Clear cell, serous, high-grade endometrioid, and mixed tumors were included. As access to tumor tissue was crucial to the goal of the parent study, as part of the inclusion criteria women had to have undergone surgical treatment as part of their primary course of therapy, which excluded the majority of the women with stage IV disease at diagnosis. Thus, we made the decision to limit the study cohort to women with stages I-III. Similarly, given that carcinosarcomas are a mixture of cell types from the inner lining endometrium and the outer muscles, our pathologists recommended excluding this subtype a priori.

We identified a total of $n = 601$ women with high grade endometrial cancers (stages I-III) who underwent a hysterectomy at KCI and HFHS between 1998 and 2017. Upon re-review of existing slides and corresponding tissue blocks, $n = 185$ (30.8%) were excluded for the following reasons: low grade ($n = 81$, 43.8%), no tumor or microscopic ($n = 70$, 37.8%), could not locate blocks ($n = 23$, 12.4%) or other reasons ($n = 23$, 12.4%). It should be noted that the large number excluded due to being of low grade does not imply that the initial report was incorrect, it could simply be that the remaining blocks did not have high grade areas, as grade is not uniform across the tumor landscape. Of the $n = 416$ remaining, $n = 34$ (8.1% of the re-confirmed high grade tumors) were excluded from the current analysis for various reasons, including death within 2 months, stage IV disease, or unknown stage.

Demographic and clinical data on patients were abstracted from the MDCSS, Detroit Medical Center (DMC), KCI, or HFHS electronic health records, spanning from 1997 to 2017. This study was approved by the Wayne State University Institutional Review Board (043116M1E).

Study variables included age at diagnosis, marital status, percentage of census tract in poverty, FIGO stage, histology, Body Mass Index (BMI) at diagnosis, comorbidity burden as measured by the Charlson Comorbidity Index, hypertension, and National Comprehensive Cancer Network (NCCN) guideline-concordant treatment. NCCN guideline-concordant treatment (NCCN GCT) was defined as a patient receiving treatment as specified by NCCN guidelines for that year, stage, and histology [13–16]. Patients receiving treatment more aggressive than recommended by NCCN were also considered guideline-concordant, with those who received less aggressive treatment than recommended by NCCN guidelines were considered not guideline-concordant. The “lead time” for adjuvant therapy was defined as the time between hysterectomy date and first adjuvant therapy treatment date (presented in months). Other categorized variables included BMI (<25.0 and 25.0+), and comorbidity count (0, 1, 2, and 3 or more; based on comorbidities included in the Charlson Comorbidity Index) [17]. Age at diagnosis was categorized (<50, 50–59, 60–69, and 70+) for use in model stratification.

Three different outcomes were assessed: overall survival, endometrial carcinoma survival accounting for the competing risk of other causes of death, and progression-free survival. Survival times were calculated from hysterectomy date to date of event or last follow-up. The outcomes were abstracted from medical records and deaths were confirmed via MDCSS and vital records. Endometrial carcinoma death was determined using the primary cause of death coded from the death certificate in the MDCSS database (ICD-10 codes: C53-C56) or from medical records. Recurrence status, used in the progression-free survival model, was ascertained through medical records by a trained SEER program abstractor. Cases were determined to be “never disease-free” when medical records indicated evidence of continued disease and/or treatment throughout the patient's survival time.

2.2. Statistical analysis

Statistical analyses were performed with SAS 9.4 (Cary, NC), figures were produced with R (version 4.0, © 2009–2020 R Studio; packages: survival, cmprsk, and survminer), and an alpha of 0.05 was considered statistically significant. The distribution of demographic and clinical variables were compared between NHW and NHB cases using chi square tests for categorical variables, Cochran-Armitage tests for ordinal variables, and Wilcoxon rank-sum tests for continuous variables. The Kaplan Meier method was used to calculate median overall and progression-free survival, along with corresponding plots. Cox proportional hazards regression was used to estimate the hazards associated with overall survival and progression-free survival. Competing risks regression using the Fine-Gray test of significance testing structure was used to analyze endometrial cancer survival with competing risk of other cause of death. Hazard ratios (HR) and 95% confidence intervals (95% CI) were reported.

The Cox model for overall survival was developed by first including all variables of interest, then excluding variables individually by highest *p*-value until all remaining variables were statistically significant. Variables were then individually reintroduced into the model to check for changes in beta estimates of 10% or more. Models were stratified by age group at diagnosis and treatment site, to account for the expectation of different baseline hazards among these subgroups. Interaction effects between factors were investigated.

The same final set of variables were utilized for the endometrial cancer-specific survival model to allow for direct comparisons of predictive variables, but includes competing risk of other cause of death.

The Cox model for progression-free survival was developed in the same manner as the model for overall survival, using the same strata to allow for varying baseline hazards. Variables were individually excluded by highest *p* value, and added back in to check for changes in beta estimates after the model included only significant variables.

3. Results

Of the 382 high grade endometrial carcinoma cases, 40.1% were NHW, and 59.9% NHB, and there were significant demographic differences between these women (Table 1). NHB women had different distributions of age group at diagnosis, marital status, and percentage of census tract in poverty when compared to NHW women. Less than 6% of NHB women were diagnosed younger than age 50, compared to 13.1% of NHW women. NHB women also had higher frequencies of being divorced, separated, or widowed (48.0% compared to 23.7% of NHW; global $p < 0.001$), and of living in a census tract with 20% or more poverty (71.6% compared to 19.6% NHW; p for trend <0.001).

Differences by race were also seen in medical history, with statistically significant differences in distribution of BMI, number of comorbidities, and hypertension. NHB women had a higher frequency of BMI over 25.0 (88.7% versus 77.8%; $p = 0.003$), having 3 or more comorbidities (16.3% versus 7.2%; $p < 0.001$), and 83.7% of NHB women had hypertension, compared to 60.5% of NHW women ($p < 0.001$). NHB and NHW women had a very similar distribution of stage at diagnosis ($p = 0.17$). As for histology, nearly 50% of NHW women were diagnosed with an endometrioid adenocarcinoma, compared to 29.7% of NHB women. Serous cell carcinoma was the predominant subtype among NHB women (54.2%). The two groups did have similar frequencies of the less common mixed cell and clear cell subtypes, but overall distributions of histologic subtypes were significantly different by race ($p < 0.001$).

While 93.9% of NHB patients received NCCN guideline-concordant treatment (GCT) compared to 91.5% of NHW women, NHB patients' median survival time was 4.7 years compared to NHW patients' 6.7 years. Both overall survival and progression-free survival showed significant differences in unadjusted survival by race (Figs. 1 and 2; log-rank *p* values = 0.008 and 0.003, respectively).

The interaction between race and BMI was a significant predictor for overall survival in both the Kaplan Meier unadjusted survival curve (Fig. 3) and the multivariable Cox proportional hazards model (Table 2); NHB women with BMI <25.0 had 3 times the hazard of death of NHW women with BMI <25.0 [HR 3.03; CI (1.35, 6.81)]. Other significant predictors that increased hazard of death included comorbidity count, not receiving NCCN guideline-concordant treatment, and later FIGO stage at diagnosis. The only histologic subtype that significantly impacted survival was the clear cell subtype, which halved hazard of death relative to the endometrioid subtype [HR 0.43, 95% CI (0.21, 0.85)].

The race/BMI interaction was also a significant predictor for endometrial carcinoma-specific survival with competing risk of other causes of death (Model 2; Table 2; Supplementary Fig. S1). NHB women with BMI <25.0 again had elevated hazard of death compared to white women in both BMI categories (HR 3.23; 95% CI [1.18, 8.85]), and compared to NHW women with BMI <25.0. As anticipated, Stage II at diagnosis more than doubled hazard of endometrial cancer death (HR 2.44; 95% CI [1.40, 4.24]) when compared to stage I patients, and hazard of endometrial cancer death was more than quadrupled in stage III patients (HR 4.52; 95% CI [3.04, 6.72]). Each additional comorbidity corresponded with a 16% higher hazard of endometrial cancer death on average (HR 1.16; 95% CI [1.03, 1.31]).

In the Cox proportional hazards model for progression-free survival, race was a statistically significant predictor, with NHB women having a 40% higher hazard of disease progression (HR 1.40; CI [1.01, 1.93]) compared to NHW women after stratification by age group and treatment site, and adjustment for stage at diagnosis, histology type, NCCN GCT, comorbidity count, and BMI category (Table 3). Patients who were stage III at diagnosis had 2.73 times the hazard of progression of stage I patients (CI [1.97, 3.79]). Comorbidity count was also a statistically significant predictor of progression, with an addition of one comorbidity corresponding with a 17% higher hazard of progression on average (HR 1.17; CI [1.06, 1.30]). Not receiving NCCN GCT more than doubled the hazard of progression (HR 2.24; CI [1.26, 4.00]), while histology and BMI were not predictive of progression-free survival.

4. Discussion

In our analysis of high grade endometrial carcinomas we find that the number of comorbid conditions, stage at diagnosis, and receiving NCCN guideline treatment are all associated with overall survival, endometrial cancer survival, and progression-free survival. The interaction of race and BMI also significantly impacts both overall survival and endometrial carcinoma-specific survival, with NHB women of low BMI having the highest risk of death even with adjustment for stage at diagnosis and histology. While other endometrial carcinoma studies that include both low and high grade tumors show a strong effect of histology on survival [18,19], histology had a minimal impact in this analysis which was restricted to high grade cases.

High BMI has been noted to increase hazard of death of endometrial cancer patients, especially for women with BMI over 40.0 [20,21,22]. A 2016 meta-analysis of studies on the impact of BMI on high and low grade endometrial cancer survival found that a 10% increase in BMI corresponded with a 9.2% increase in the odds of all-cause mortality [20]. Obesity is a known risk factor for development of all subtypes of endometrial cancer [3], although it's more closely linked with the endometrioid subtype than others, possibly due a stronger link between circulating estrogen levels [5,21]. While studies of the association between BMI and survival in endometrial cancer patients have been mixed [21,23], most did not consider subtype and race concurrently. Here, we found that black women with BMI under 25.0 had the highest hazard of death compared to women of either race with a BMI of 25.0 or more. Only 12% of NHB women had BMI below 25, so we were unable to determine how the disease course in these women may differ from their overweight and obese counterparts. While white women with BMI less than 25.0 had a survival advantage, black women with BMI less than 25.0 had the poorest overall survival and endometrial cancer survival; this observed paradox warrants further investigation into this interaction of race and BMI and its effects on survival.

Often coinciding with obesity, comorbidities play a role in endometrial cancer survival and progression, as they do in other cancers [24,25]. As both endometrial cancer and comorbidities are more common among older people [24], comorbidities impact both treatment options and survival. A 2017 cohort study found that among over 1000 early-stage endometrial cancer patients, 78% of patients that died within 10 years of surgical treatment (hysterectomy) had a cause of death other than endometrial cancer [26]. A national report from 2014 found that 40% of cancer patients on Medicare had at least one other chronic condition, and 15% had 2 or more, although this report did not include observations by race [24]. Similarly, in our study population, comorbidities were present in 40% of NHW patients and 60% of NHB patients. Multiple studies have reported that patients with comorbidities are less likely to

Table 1
Descriptive statistics for high grade endometrial cancer cases at Henry Ford Hospital and Karmanos Cancer Institute (diagnosed 1997–2017) by race.

Characteristic	All (N = 382)	Race		P value[a]
		Non-Hispanic White (N = 153)	Non-Hispanic Black (N = 229)	
Demographics				
Age at diagnosis				
Mean (Std)	63.4 (9.1)	62.0 (10.0)	64.3 (8.4)	0.006
Median (Range)	65.0 (48.0)	64.0 (48.0)	65.0 (42.0)	
Age at diagnosis (categories)				
<50 years	33 (8.6)	20 (13.1)	13 (5.7)	0.01
50–59 years	80 (20.9)	36 (23.5)	44 (19.2)	
60–69 years	165 (43.2)	60 (39.2)	105 (45.9)	
70+ years	104 (27.2)	37 (24.2)	67 (29.3)	
Marital status[b]				
Never married	70 (18.6)	24 (16.5)	46 (20.4)	<0.001
Married/Living with Partner	162 (43.1)	91 (59.9)	71 (31.6)	
Separated/Divorced/Widowed	144 (38.3)	36 (23.7)	108 (48.0)	
Census Tract % in poverty				
0–5%	55 (14.4)	47 (30.7)	8 (3.5)	<0.001
5–10%	52 (13.6)	42 (27.5)	10 (4.4)	
10–20%	81 (21.2)	34 (22.2)	47 (20.5)	
20–100%	194 (50.8)	30 (19.6)	164 (71.6)	
Diagnosis				
Stage at diagnosis				
I	201 (52.6)	85 (55.6)	116 (50.7)	0.17
II	50 (13.1)	14 (9.2)	36 (15.7)	
III	131 (34.3)	54 (35.3)	77 (33.6)	
Histologic subtype				
Clear cell	27 (7.1)	10 (6.5)	17 (7.4)	<0.001
Endometrioid	144 (37.7)	76 (49.7)	68 (29.7)	
Mixed cell	36 (9.4)	16 (10.5)	20 (8.7)	
Serous	175 (45.8)	51 (33.3)	124 (54.2)	
Medical history				
Body mass index				
<25.0	60 (17.1)	34 (24.5)	26 (12.3)	0.003
>25.0	322 (84.3)	119 (77.8)	203 (88.7)	
Comorbidity count				
None	187 (49.3)	94 (61.8)	93 (41.0)	<0.001
1	102 (26.9)	35 (23.0)	67 (29.5)	
2	42 (11.1)	12 (7.9)	30 (13.2)	
3 or more	48 (12.7)	11 (7.2)	37 (16.3)	
Hypertension				
Yes	282 (74.4)	92 (60.5)	190 (83.7)	<0.001
No	97 (25.6)	60 (39.5)	37 (16.3)	
NCCN Guideline-Concordant Treatment[c]				
Yes	355 (92.9)	140 (91.5)	215 (93.9)	0.37
No	27 (7.1)	13 (8.5)	14 (6.1)	
Adjuvant therapy				
None (Surgery only)	101 (26.4)	35 (22.9)	66 (28.8)	0.51
Chemo only	59 (15.5)	24 (15.7)	35 (15.3)	
Radiation only	121 (31.7)	54 (35.3)	67 (29.3)	
Chemo + Radiation	101 (26.4)	40 (26.1)	61 (26.6)	
Adjuvant Therapy Lead Time[d]				
<3 Months	154 (67.3)	66 (70.2)	88 (65.2)	0.52
≥3, <6 Months	52 (22.7)	19 (20.2)	33 (24.4)	
≥6 Months	23 (10.0)	9 (9.6)	14 (10.4)	
Vital Status				
Living	179 (46.9)	82 (53.6)	97 (42.4)	0.03
Dead	203 (53.1)	71 (46.4)	132 (57.6)	
Overall survival time				
<5 years	177 (46.3)	57 (37.3)	120 (52.4)	0.003
5 years or more	205 (53.7)	96 (62.8)	109 (47.6)	
Overall survival time (years)[e]				
Median	5.7	6.7	4.7	0.002
Endometrial cancer survival				
Alive	179 (46.9)	82 (53.6)	97 (42.4)	0.09
Death by endometrial cancer	141 (36.9)	48 (31.4)	93 (40.6)	
Death by other cause	62 (16.2)	23 (15.0)	39 (17.0)	
Recurrence status [1]				
No recurrence	230 (61.2)	103 (69.1)	127 (56.0)	0.03
Recurrence	107 (28.5)	32 (21.5)	75 (33.0)	
Never Disease-free	39 (10.4)	14 (9.4)	25 (11.0)	
Progression free survival time (years)[e]				
Median	4.9	6.4	3.9	0.03

Abbreviations: NCCN (National Cancer Care Network)

[a] calculated with Wilcoxon test for continuous variables, Cochran Armitage test for ordinal variables, Chi squared tests for categorical variables, and median one-way analysis for survival time variables

[b] N unknown = 6

[c] N unknown = 5

[d] Time between hysterectomy date and first adjuvant therapy treatment date, N unknown date = 52

[e] Calculated with Kaplan Meier

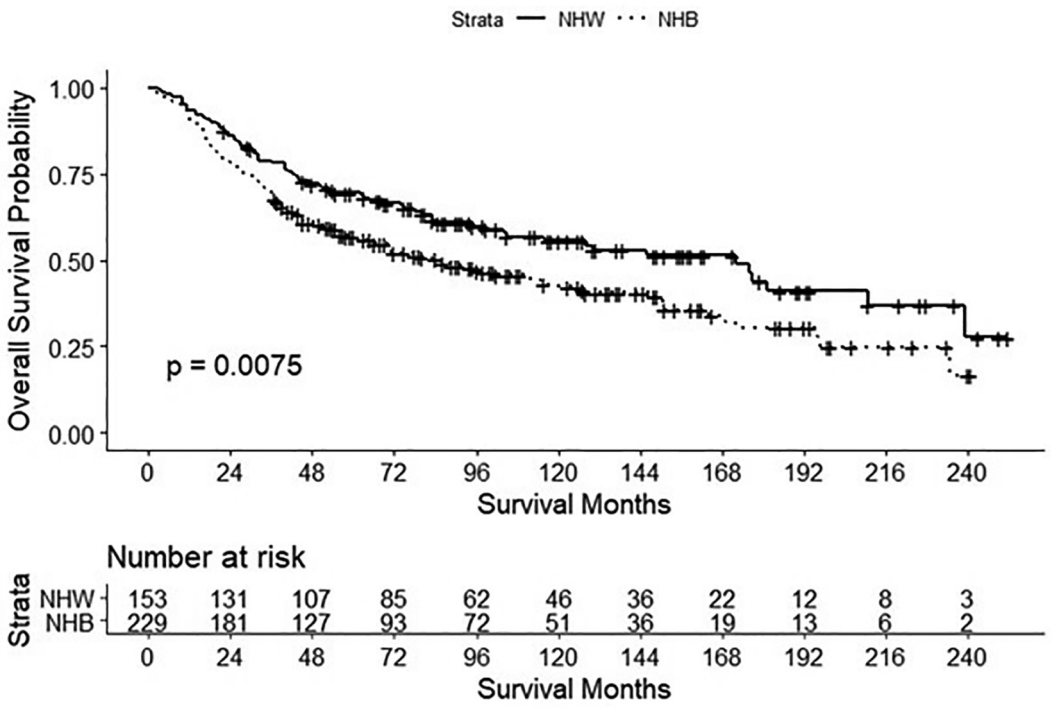

Fig. 1. Overall Survival by Race. Kaplan Meier overall survival for the 382 high grade endometrial carcinoma cases after surgery, by race. Race is an independent predictor of overall survival in unadjusted analysis ($p = 0.0075$). Abbreviations: non-Hispanic white (NHW), non-Hispanic black (NHB).

receive curative treatment for their cancer, due to factors such as contraindications for treatment [24,25]. Our analysis shows that receipt of NCCN guideline-concordant treatment is associated with improved overall survival, disease-specific survival, and progression-free survival. We also report no differences in receipt of NCCN guideline-concordant care by race in our population, all receiving care at high-volume academic institutions. The percentages of women receiving guideline-concordant care in our study is higher than what has been reported in other US study cohorts [27,28].

Previous research on high grade endometrial cancer has had mixed results regarding the effect of histologic subtype on survival. In particular, the endometrioid subtype has been associated with improved survival compared to other high grade subtypes in a study using data from all SEER sites, as well as the National Cancer Database [29–31].

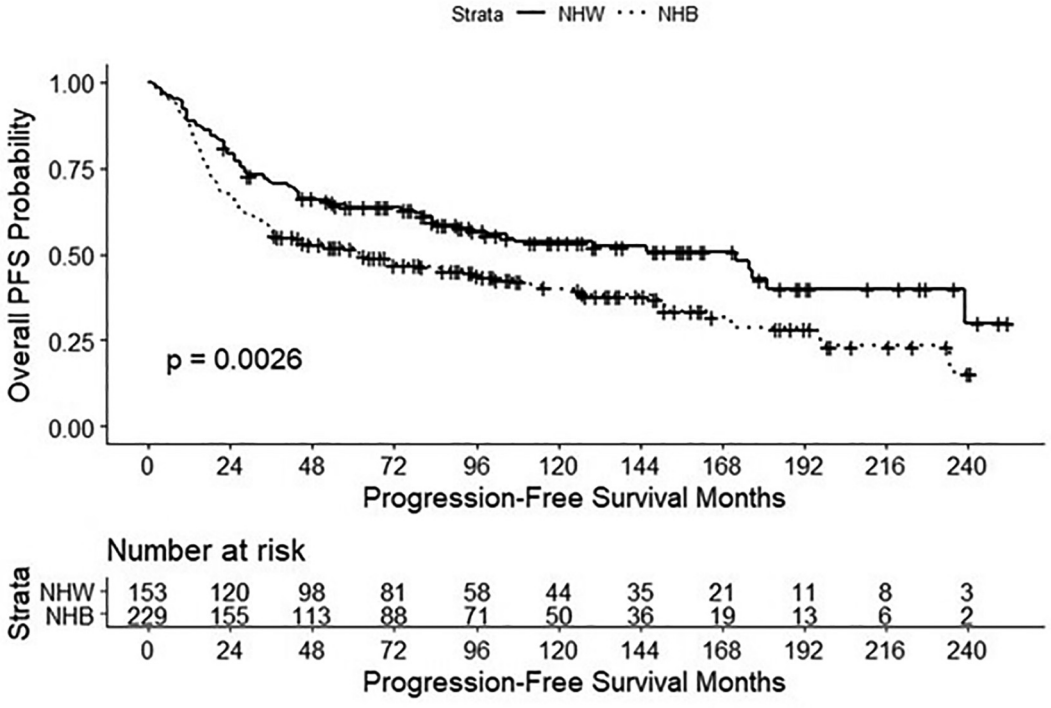

Fig. 2. Progression-Free Survival by Race: Kaplan-Meier progression-free survival for the 382 high grade endometrial carcinoma cases after surgery, by race (NHW and NHB). Race is an independent predictor of progression-free survival in this unadjusted analysis ($P = 0.0016$). Abbreviations: NHW (non-Hispanic white), NHB (non-Hispanic black).

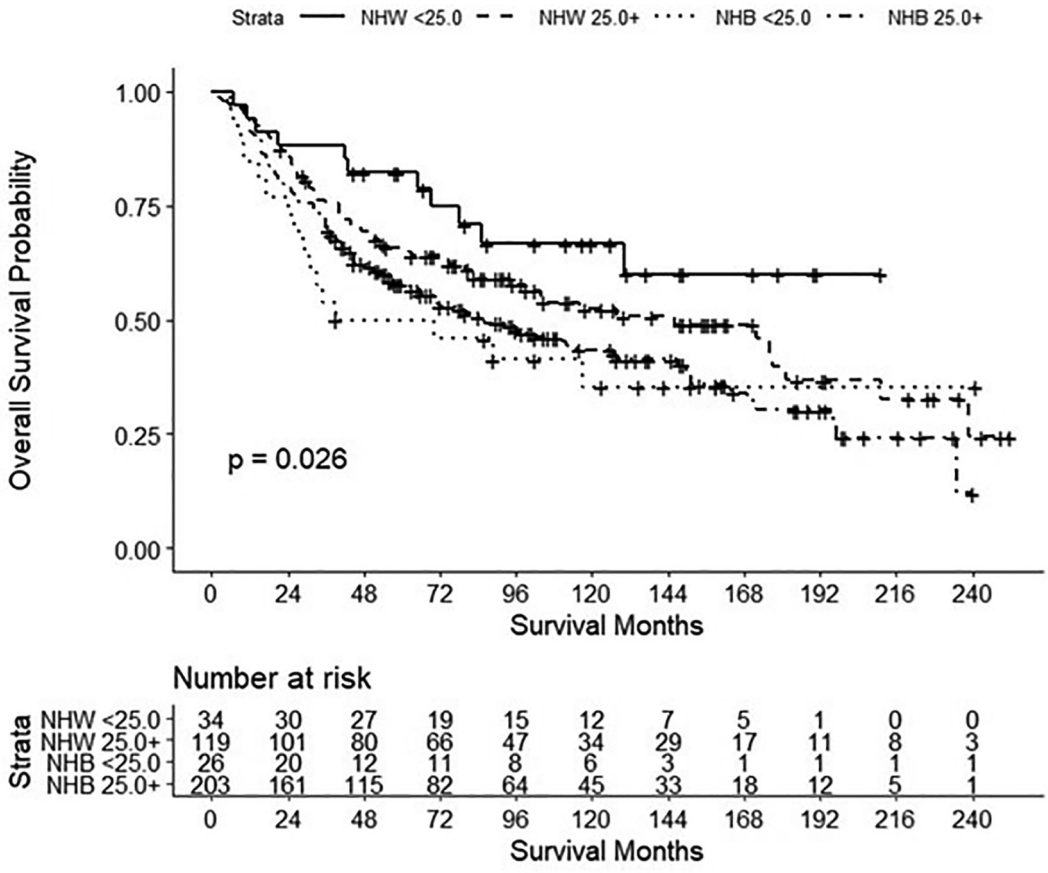

Fig. 3. Overall Survival by Race and BMI. Kaplan-Meier overall survival for the 382 high grade endometrial cancer cases after surgery, by race and BMI (NHW <25.0, NHW 25.0+, NHB <25.0, NHB 25.0+). The race/BMI interaction is an independent predictor of progression-free survival in this unadjusted analysis ($P = 0.024$). Abbreviations: NHW (non-Hispanic white), NHB (non-Hispanic black), BMI (body mass index).

Table 2
Cox proportional hazards models for high grade endometrial cancer survival (diagnosed 1997–2017).

	Model 1.		Model 2.	
	Death by any cause / Overall survival		Endometrial cancer death with competing risk of death by other cause	
Covariate	HR (95% CI)	P value	HR (95% CI)	P value
Race and BMI				
NHW BMI <25.0	Ref		Ref	
NHW BMI 25.0+	2.17 (1.10, 4.29)	0.03*	2.32 (0.93, 5.37)	0.07
NHB BMI <25.0	3.03 (1.35, 6.81)	0.004*	3.23 (1.18, 8.85)	0.02*
NHB BMI 25.0+	2.43 (1.28, 4.60)	0.006*	2.56 (1.10, 5.95)	0.03*
FIGO stage at diagnosis				
Stage I	Ref		Ref	
Stage II	1.64 (1.03, 2.63)	0.04*	2.44 (1.40, 4.24)	0.002*
Stage III	3.28 (2.37, 4.53)	<0.001*	4.52 (3.04, 6.72)	<0.001*
Histologic subtype				
Endometrioid	Ref		Ref	
Clear Cell	0.43 (0.21, 0.85)	0.02*	0.44 (0.20, 1.01)	0.05
Mixed	1.06 (0.62, 1.80)	0.83	1.07 (0.57, 2.01)	0.84
Serous	0.95 (1.01, 0.73)	0.95	1.11 (0.75, 1.64)	0.59
NCCN GCT				
Yes	Ref		Ref	
No	2.52 (1.50, 4.26)	<0.001*	3.00 (1.64, 5.47)	<0.001*
Comorbidity count	1.23 (1.12, 1.36)	<0.001*	1.16 (1.03, 1.31)	0.01*

Abbreviations: NHW (non-Hispanic white); NHB (non-Hispanic black); BMI (body mass index); NCCN GCT (National Cancer Care Network Guideline-Concordant Treatment)
* Statistically significant at $\alpha = 0.05$

Table 3
Cox proportional hazards model for progression-free survival of high grade endometrial cancer cases (diagnosed 1997–2017).

Covariate	HR (CI)	P value
Patient race		
NHW	Ref	
NHB	1.40 (1.01, 1.93)	0.05*
Stage at diagnosis		
I	Ref	
II	1.55 (0.96, 2.49)	0.07
III	2.73 (1.97, 3.79)	<0.001*
Histologic subtype		
Endometrioid	Ref	
Clear Cell	0.57 (0.30, 1.10)	0.10
Mixed	1.14 (0.67, 1.93)	0.63
Serous	1.14 (0.81, 1.59)	0.45
NCCN GCT		
Yes	Ref	
No	2.24 (1.26, 4.00)	0.01*
Comorbidity count	1.17 (1.06, 1.30)	0.002*
Body mass index		
<25.0	Ref	
>25.0	1.23 (0.81, 1.86)	0.33

Abbreviations: NHW (non-Hispanic white); NHB (non-Hispanic black); NCCN GCT (National Cancer Care Network Guideline-Concordant Treatment
* statistically significant at $\alpha = 0.05$

A California SEER-based study found that disease-specific survival in women with high grade tumors was similar for serous, clear cell, and endometrioid cancers [32]. Other studies focused on high grade endometrial cancer suggest that the conventional histologic subtyping is too limited, and that incorporating molecular and genetic markers into tumor classification, along with histologic subtyping and grading will ultimately provide better insight into prognosis and treatment [33].

Our study has a number of strengths, including the utilization of both medical records and cancer registry data to focus on high grade endometrial carcinomas. Next, often underrepresented in endometrial carcinoma research despite historically worse outcomes, 60% of our study population is NHB, which is representative of the metropolitan Detroit population served by KCI and HFHS. In addition, with tissue blocks available, we were able to have each case reviewed by our pathologist for FIGO histologic grade and subtype. Lastly, the retrospective design of the study allowed for each patient to be followed for at least 5 years, which is sufficient to identify most recurrences and deaths in women with high grade endometrial carcinomas.

There are limitations that should be noted, including the hospital-based design that included only women with hysterectomies after an endometrial carcinoma diagnosis from two urban academic cancer centers. This excluded stage 4 cancers, those who did not receive surgical treatment, as well as carcinosarcomas, which are also aggressive endometrial cancers. Thus, this limits the generalizability of these results, although the vast majority of women with an endometrial carcinoma diagnosis receive a hysterectomy. Additionally, while both medical records and death certificates were reviewed for cause of death, it is possible that endometrial carcinoma-related deaths were underreported on the death certificates. Finally, as this was a retrospective analysis, we were unable to assess some factors that are likely associated with endometrial carcinoma survival, including access to care, subsequent treatment, economic status and education, and health behaviors (e.g., smoking) that may play a role in survival. Prospective work to understand how social determinants of health, medical mistrust, and economic factors, often the result of decades of structural barriers, interact with biological variables that impact endometrial carcinoma outcomes is needed to eliminate the current disparities seen in survival in most population-based studies.

As with many cancers, a focus on primary care and prevention of chronic conditions can reduce cancer risk and increase odds of survival if a patient is to develop cancer. Prevention of comorbidities may increase the percentage of patients that are able to receive NCCN guideline-concordant care, especially important in aggressive cancers such as these high grade endometrial carcinomas. Additional research is underway into the genomic landscape of high grade endometrial carcinomas and may provide a variety of targeted therapies that will improve outcomes for all women with these aggressive tumor subtypes.

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Author contribution

Juliana Fucinari: Data curation, Formal Analysis, Visualization, Writing - Original Draft.

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Declaration of Competing Interest

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