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Association of obesity with survival in patients with endometrial cancer☆

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HIGHLIGHTS

- In women with endometrial cancer there are differences in histology and race associated with obesity.
- Increased obesity is associated with younger age at endometrial cancer diagnosis.
- Obesity may have a protective effect on higher stage non-endometrioid endometrial cancer.

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ABSTRACT

Background. Obesity confers an overall increased risk for development of endometrial cancer. However there are conflicting reports regarding the effect of obesity on patients' overall and disease specific survival. The purpose of this study was to evaluate the effect of obesity on survival in women with endometrial cancer.

Methods. After IRB approval, records of women with diagnosis and treatment of endometrial cancer from 1999 to 2016 were abstracted for histopathological, treatment and demographic data. Death was confirmed by query of the Social Security Death Index. Kaplan Meier survival curves and Cox regression modeling was performed with Stata version 14.0.

Results. Of 1732 evaluable patients, there were significant differences in age at diagnosis, histology (endometrioid versus non-endometrioid), stage, race, grade, hypertension, hyperlipidemia, diabetes, and treatment between normal weight, overweight, obese, and morbidly obese patients ($p < 0.01$). There was a linear association of younger age at diagnosis with increasing obesity ($p < 0.01$) $R^2 = 0.04$. Younger age, endometrioid histology, lower stage, and statin use were independently associated with decreased hazard of death ($p < 0.01$). However, in stratified analysis of non-endometrioid histologies, patients with Stage 3 and 4 disease over the age of 65 showed a survival benefit for women associated with obesity ($p = 0.02$).

Conclusions. Obesity is associated with younger age at diagnosis and earlier stage disease. Obesity is associated with improved disease specific survival for stage 3 and 4 non-endometrioid endometrial cancers.

1. Background

The association between obesity and development of endometrioid endometrial cancers has been well established, and there has been recent data suggesting that obesity is a risk factor for non-endometrioid endometrial cancers [1–3]. Up to 80% of endometrial cancer risk has been attributed to body mass index (BMI), physical activity and diet [4]. In the general population of healthy women, disease specific mortality from endometrial cancer has been reported as 6.25-fold higher (95% confidence interval (CI) 3.75–10.42) in the comparison of obese versus non-obese women with obesity defined as BMI ≥ 40 kg/m^2 [5]. The impact of obesity on mortality including disease specific and overall survival, for endometrial cancer survivors is controversial.

The impact of morbid obesity on endometrial cancer survivors has been reported from several centers using different methodologies and with opposite conclusions. These conclusions include improved survival, no association with survival and worsened survival associated with obesity depending on the population sampled, methodology of BMI comparison, and control for other variables. Obesity was described as conferring a favorable prognosis by prolonged progression free and overall survival by Anderson et al., and Munstedt et al. respectively [6,7]. Similarly, Mauland et al. and Jeong et al. found significantly better

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disease specific survival, for obese patients on univariate analysis but that it was not significant after multivariable control for age, FIGO Stage, subtype and grade [8,9]. A recent study of 154 women with high-risk endometrial cancer, failed to show an association with BMI, progression free survival, or overall survival, in a population of women characterized by 78% with BMI > 25 kg/m^2 [10].

Conversely several studies have reported 1.6–2.9 increased hazard of death, including disease specific and overall for patients with elevated BMI verses patients of normal weight with endometrial cancer [11]. Additionally, endometrial cancer survivors with BMI > 40 were reported to have decreased overall survival as compared to BMI <30 (HR 2.77; 95% CI 1.21–6.36 $p = 0.16$) in a Gynecologic Group Study [11]. In a pooled analysis of patients enrolled in 5 Gynecologic Oncology Group trials receiving cisplatin and doxorubicin there was no association of BMI with progression free survival for women receiving doxorubicin and platinum as part of GOG trials overall, but decreased overall survival for women with stage 3 or 4 disease and higher BMI [12]. Survivors with BMI ≥ 30 kg/m^2 were reported to have higher all cause (HR 1.6, 95% CI 1.0–2.5) and disease specific (HR 2.0, 95% CI 0.8–5.1) mortality as compared to non-obese survivors by Chia et al. [13]. After stratification for poor risk factor including high stage, high grade, deep myometrial invasion as defined by >50% invasion, cervical involvement, lymph node metastases, positive cytology, and lymphvascular space invasion Gates et al. also reported poorer survival for overweight verses normal weight survivors [14]. Felix et al. from a study of 4609 women enrolled in the GOG 210 trial reported decreased survival for women with Class II obesity to normal BMI (HR2.29, 95% CI = 1.06–4.98, $p = 0.01$) [15]. In these studies the majority of participants were of white race and non-Hispanic ethnicity.

The purpose of this study was to report the association of obesity with survival of women with both endometrioid and non-endometrioid cancers in a racially and ethnically diverse population. Secondarily, the goal of this study was to evaluate the association of race, and the use of antihyperlipidemic/antihypglycemic/anti-inflammatory medications with obesity and survival.

2. Methods

After Internal Review Board approval all women treated for endometrial cancer from 1999 to 2016 at Montefiore Medical Center were reviewed for histopathological, treatment and demographic data. Data collected included age at histopathological diagnosis, stage, grade, histology, self-identified race/ethnicity, medical comorbidities, medication use, treatment, and date of last contact. Body mass index (BMI) was measured in kilograms per meter squared and categories of BMI were designated as underweight < 18.5, normal 18.5–24.9, overweight 25–29.9, class I obese 30–34.9, class II obese 35–39.9, class III obesity ≥ 40. Type 2 or non-endometrioid cancers were defined as serous, carcinosarcomas, clear cell, mixed and poorly differentiated. Any percentage of serous, carcinosarcoma, clear cell, mixed or poorly differentiated tumor qualified as classification into that respective histological category. Death was confirmed by query of the Social Security Death Index. Disease specific survival (DSS) was defined as the interval from time of histopathologically confirmed cancer from biopsy or surgical resection to death attributable to uterine malignancy. Overall survival (OS) was defined as the interval from diagnosis to death by any cause. For patients who were still alive at the time of analysis, DSS and OS were censored at the date of follow up.

Demographic, histopathologic and medical data were presented as face valid terms and univariable analysis was performed to identify differences between obesity categories. Linear regression modeling was performed for BMI categories and associated age at diagnosis. DSS and OS by BMI category were summarized for the entire cohort, endometrioid, and non-endometrioid patients separately using Kaplan-Meier survival curves. Univariable, multivariable and stratified Cox regression modeling were performed to assess the independent association of BMI on survival. The cohort was analyzed as a whole and then separate sub-cohorts of endometrioid histology only, non-endometrioid or Type II histology for distribution of characteristics including race and obesity and then univariable and multivariable Cox regression modeling was conducted for the entire cohort and histologic sub-cohorts. All possible factors associated with both BMI and disease-specific mortality and those found to have $p < 0.10$ in univariable analysis were included in the multivariable model. Variables with evidence of collinearity were excluded from the model as described.

In a sub-cohort of patients with endometrioid (Type I) lesions confined to the uterus, evaluation of high risk factors including depth of invasion, lymph vascular space invasion, and grade of tumor were evaluated for their association with obesity. Additionally, estrogen receptor and progesterone receptor status were obtained when available from the pathology report and univariable and multivariable modeling was performed to identify any association of obesity as measured in kilograms per meter-squared with high risk factors and with race. Progesterone and estrogen receptor positive was defined by institutional pathology standard of ≥20%. Testing for Lynch syndrome and microsatellite stability was also obtained from the pathology record. All analyses were performed using Stata version 14.0 (StataCorp. 2015. *Stata Statistical Software*: *Release 14*. College Station, TX: StataCorp LP.)

3. Results

1868 women were treated for endometrial cancer at Montefiore Medical Center from 1999 to 2016. Nineteen patients with BMI < 18.5 kg/m^2 and 115 patients with missing BMI data at diagnosis were excluded from the analysis. There were 1732 evaluable records with complete data including BMI included in the cohort. BMI categories of the cohort included 357 (19%) Class III obesity, 267 (14%) Class II obesity, 458 (25%) Class I obesity, 417 (22%) overweight, and 233 (13%) normal weight (Table 1). 1107 (64%) had endometrioid endometrial cancers, and 625 (36%) had non-endometrioid endometrial cancers. Of the 625 non-endometrioid cancers there were 413(66%) serous, 142 (23%) carcinosarcomas, 35 (5%) clear cell, and 36 (6%) mixeed or poorly differentiated. 504 (29%) were white, 588 (34%) were black, 487 (28%) were Hispanic, 60 (3%) were Asian and 46 (3%) were other by self-defined racial ethnic category. 911 did not receive adjuvant therapy with chemotherapy and/or radiation. 490 (28%) had diabetes, 616 (36%) had hyperlipidemia and 578 (34%) had hypertension.

On bivariate analysis, significant differences were noted across BMI categories in age at diagnosis, histology, stage, race, grade, hypertension, hyperlipidemia, diabetes, and treatment modalities (Table 1). Overall, there was a significant inverse linear association of age at diagnosis with BMI ($p < 0.001$, $R^2 = 0.04$) (Fig. 1). As expected, women with endometrioid histology had a younger age at diagnosis than women with non-endometrioid histologies. The inverse linear association was observed in both subgroups ($p < 0.001$, Fig. 1). Significant differences ($p < 0.05$) associated with higher BMI in the endometrioid subgroup included uterine confined disease at diagnosis, grade 1 tumors, non-white race, diagnosis of hypertension, and no further adjuvant treatment (Supplementary Table 1). Stage was not associated with BMI in women with non-endometrioid histology.

In the cohort of evaluable patients for this analysis, 543 women had died overall, 393 (22.7%) from disease specific causes. Median follow up was 3.4 years [Range: 1 day–17.8 years] for the entire cohort, 4.3 years [Range: 1 day–17.8 years] for endometrioid cancers, and 2.1 years [Range: 10 days–17.4 years] for non-endometrioid cancers. There was a significant difference in disease specific and overall survival curves and trend across BMI categories (log rank test $p < 0.001$, test of trend $p < 0.001$) (Fig. 2) for the entire cohort. In univariable analysis, younger age at diagnosis, higher BMI, endometrioid histological subtype, lower stage, white race, lower grade, hyperlipidemia, statin use, metformin use, beta blocker use, and adjuvant therapy were associated with decreased hazard of disease specific death ($p < 0.01$) (Table 2). In

Table 1
Demographic, histopathologic and treatment variables by BMI category of women treated for endometrial cancer.

Variable	Cohort $N = 1732$	Normal 18.5–24.9 $N = 233$	Overweight 25–29.9 $N = 417$	Obese 30–34.9 $N = 458$	Obese 35–39.9 $N = 267$	Morbidly obese > 40 $N = 357$	p-Value*
Age (years)	64.0 (11.2)	67.8 (11.2)	65.4 (11.4)	64.2 (10.8)	62.4 (11.1)	60.6 (9.8)	<0.001
Histology							<0.001
Type 1	1107 (63.7)	115 (48.9)	246 (59.0)	279 (60.9)	185 (69.3)	282 (79.0)	
Type 2	625 (36.3)	118 (51.1)	171 (41.0)	179 (39.1)	82 (30.7)	75 (21.0)	
Stage							<0.001
I	1197 (69.2)	129 (54.9)	273 (65.6)	312 (68.1)	191 (72.1)	292 (81.8)	
II	114 (6.6)	20 (8.5)	29 (7.0)	38 (8.3)	15 (5.7)	12 (3.4)	
III	199 (11.5)	38 (16.2)	56 (13.5)	47 (10.3)	29 (10.9)	29 (8.1)	
IV	172 (9.9)	42 (17.9)	43 (10.3)	48 (10.5)	22 (8.3)	17 (4.8)	
Unstaged	49 (2.8)	6 (2.6)	15 (3.6)	13 (2.8)	8 (3.0)	7 (2.0)	
Stage							<0.001
I/II	1311 (77.9)	149 (65.1)	302 (75.3)	350 (78.7)	206 (80.2)	304 (86.9)	
III/IV	371 (22.1)	80 (34.9)	99 (24.7)	95 (21.3)	51 (19.8)	46 (13.1)	
Race/Ethnicity							<0.001
White	504 (29.9)	81 (35.4)	124 (30.6)	130 (29.4)	63 (24.1)	106 (30.6)	
Black	588 (34.9)	76 (33.2)	119 (29.4)	159 (35.9)	105 (40.1)	129 (37.3)	
Hispanic	487 (28.9)	45 (19.7)	124 (30.6)	135 (30.5)	82 (31.3)	101 (29.2)	
Asian	60 (3.6)	22 (9.6)	22 (5.4)	11 (2.5)	2 (0.8)	3 (0.9)	
Other	46 (2.7)	5 (2.2)	16 (4.0)	8 (1.8)	10 (3.8)	7 (2.0)	
Grade							<0.001
1	750 (43.3)	67 (28.5)	154 (37.0)	182 (39.7)	134 (50.6)	213 (59.7)	
2	252 (14.6)	26 (11.1)	73 (17.6)	70 (15.3)	29 (10.9)	54 (15.1)	
3	729 (42.1)	142 (60.4)	189 (45.4)	206 (45.0)	102 (38.5)	90 (25.2)	
Hypertension	578 (33.5)	130 (55.8)	250 (60.2)	308 (67.4)	195 (73.4)	265 (74.4)	<0.001
Hyperlipidemia	616 (35.7)	70 (30.0)	137 (33.0)	185 (40.6)	108 (40.6)	116 (32.6)	0.009
Diabetes	490 (28.4)	37 (15.9)	100 (24.1)	135 (29.5)	91 (34.2)	127 (35.7)	<0.001
Medications							
Statin	517 (32.4)	57 (27.9)	114 (30.0)	156 (36.5)	89 (35.3)	101 (30.3)	0.10
Aspirin	331 (20.7)	39 (19.1)	75 (19.8)	101 (23.5)	47 (18.7)	69 (20.7)	0.52
Metformin	265 (16.7)	20 (9.8)	50 (13.2)	80 (18.7)	49 (19.4)	66 (19.8)	0.004
Beta blocker	439 (27.5)	58 (28.4)	104 (27.4)	113 (26.3)	70 (27.8)	94 (28.2)	0.98
Treatment							<0.001
No Chemo/RT	911 (52.7)	95 (40.4)	204 (49.0)	226 (49.7)	143 (53.6)	243 (68.3)	
Chemo only	188 (10.8)	41 (17.5)	48 (11.5)	50 (11.0)	25 (9.4)	24 (6.7)	
RT only	193 (11.2)	23 (9.8)	51 (12.2)	62 (13.6)	29 (10.8)	28 (7.9)	
Chemo/RT	438 (25.3)	76 (32.3)	114 (27.3)	117 (25.7)	70 (26.2)	61 (17.1)	

* ANOVA, Pearson's Chi-squared, or Fisher Exact as appropriate.

multivariable analysis, younger age, lower stage, lower grade, and use of statins and metformin were independently associated with decreased hazard of disease-specific death ($p < 0.05$). Hyperlipidemia and statin use were deemed to be collinear ($\rho = 0.91$, variance inflation factor (VIF) > 5) and hyperlipidemia was subsequently excluded from the chosen model in order to retain possible associations of medication use. After controlling for other factors, BMI overall was not associated with disease-specific death (Wald $p = 0.10$). However, in multivariable analysis comparing women with Class 2 obesity to normal weight women there was a decreased hazard of death for women with Class 2 obesity (HR 0.65; 95% CI 0.2–0.97, $p = 0.04$).

In the subgroup of women with endometrioid histology there remained a difference in overall and disease specific survival curves on Kaplan Meier analysis (log rank $p = 0.03$, Supplementary Fig. 1). In univariable analysis of this subgroup, age, BMI, stage, grade, hyperlipidemia, and use of beta blockers, were associated with improved disease-specific survival ($p < 0.05$). Diabetes and need of any adjuvant therapy (chemotherapy, radiation therapy or both) were associated with increased hazard of death for patients with endometrioid histology by univariable analysis. In multivariable analysis, independent predictors of improved disease-specific survival for patients with endometrioid cancers included younger age at diagnosis, earlier stage disease, low

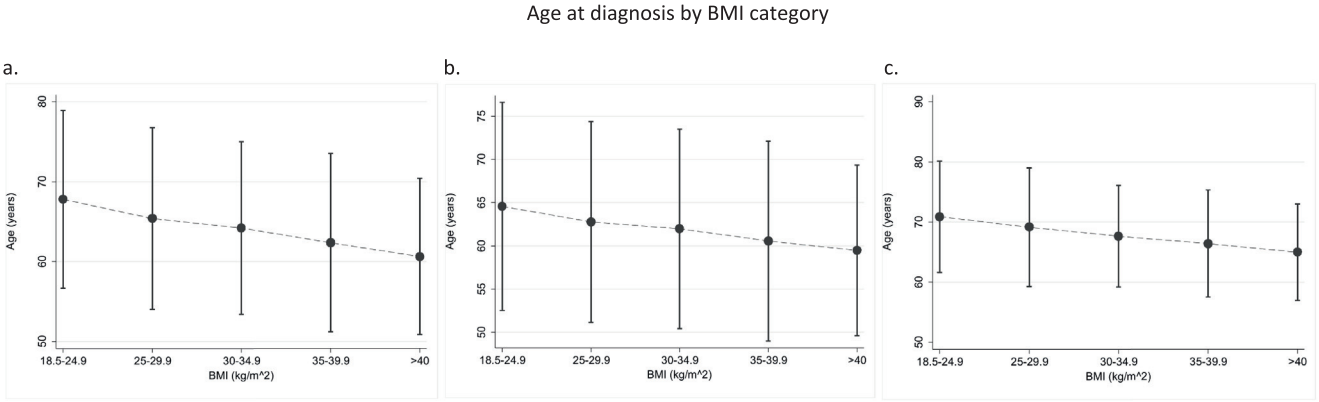

Fig. 1. Linear association of younger age at diagnosis with increased BMI. (A. entire cohort; B. endometrioid histology; C. non-endometrioid histology). Bars reflect 95% confidence intervals.

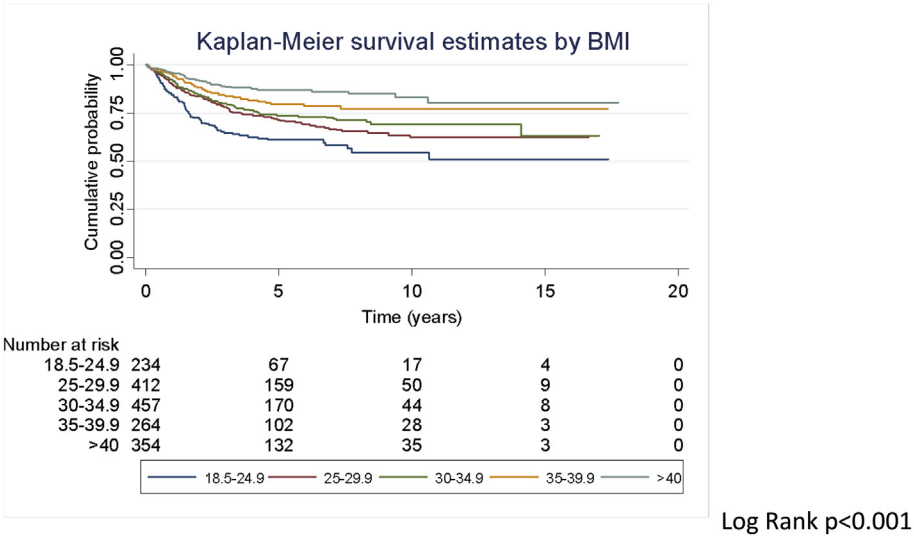

Fig. 2. Kaplan–Meier overall survival estimates by body mass index for women with endometrial cancer.

Table 2
Multivariable Cox Regression Modeling of hazard for disease specific death for women with endometrial cancer.

Variable	Univariable hazard ratio (95% CI, *p*-value)	Multivariable hazard ratio[3] (95% CI, *p*-value)
Age (years)	1.05 (1.04–1.06, <0.001)	1.02 (1.01–1.03, <0.001)
BMI (kg/m^2)	Overall Wald $p < 0.001$	Overall Wald $p = 0.10$
Normal 18.5–24.9	1.00 (reference)	1.00 (reference)
Overweight 25–29.9	0.67 (0.50–0.89, 0.006)	0.97 (0.70–1.34, 0.87)
Obese 30–34.9	0.57 (0.43–0.76, <0.001)	1.00 (0.72–1.37, 0.98)
Obese 35–39.9	0.42 (0.29–0.60, <0.001)	0.65 (0.44–0.97, 0.04)
Morbid obese ≥ 40	0.28 (0.19–0.41, <0.001)	0.74 (0.49–1.11, 0.14)
Histology		
Type 1	1.00 (reference)	1.00 (reference)
Type 2	7.00 (5.56–8.81, <0.001)	1.00 (0.65–1.55, 0.99)
Stage	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$
I	1.00 (reference)	1.00 (reference)
II	4.19 (2.86–6.14, <0.001)	2.68 (1.77–4.06, <0.001)
III	7.67 (5.73–10.27, <0.001)	4.30 (3.08–5.99, <0.001)
IV	24.80 (18.94–32.47, <0.001)	9.96 (6.93–14.32, <0.001)
Unstaged	13.08 (8.62–19.85, <0.001	11.38 (7.25–17.86, <0.001)
Stage		
I/II	1.00 (reference)	
III/IV	10.28 (8.25–12.80, <0.001	
Race/Ethnicity	Overall Wald $p < 0.001$	Overall Wald $p = 0.16$
White	1.00 (reference)	1.00 (reference)
Black	1.95 (1.53–2.50, <0.001)	0.99 (0.75–1.31, 0.96)
Hispanic	0.99 (0.74–1.32, 0.94)	0.75 (0.55–1.02, 0.07)
Asian	0.58 (0.24–1.43, 0.24)	0.58 (0.23–1.45, 0.25)
Other	0.72 (0.33–1.55, 0.40)	0.67 (0.28–1.57, 0.36)
Grade	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$
1	1.00 (reference)	1.00 (reference)
2	2.72 (1.69–4.40, <0.001)	1.77 (1.05–2.98, 0.03)
3	12.27 (8.65–17.40, <0.001)	4.20 (2.47–7.12, <0.001)
Hypertension	0.96 (0.78–1.19, 0.70)	
Hyperlipidemia	0.56 (0.45–0.71, <0.001)	
Diabetes	0.81 (0.64–1.02, 0.07)	1.34 (0.99–1.83, 0.06)
Medications		
Statin	0.57 (0.44–0.73, <0.001)	0.55 (0.42–0.72, <0.001)
Aspirin	0.96 (0.74–1.24, 0.73)	
Metformin	0.57 (0.41–0.81, 0.001)	0.65 (0.42–1.00, 0.05)
Beta Blocker	1.25 (1.00–1.57, 0.05)	1.20 (0.94–1.53, 0.14)
Treatment	Overall Wald $p < 0.001$	Overall Wald $p = 0.02$
No Chemo/RT	1.00 (reference)	1.00 (reference)
Chemo only	9.75 (7.36–12.93, <0.001)	1.54 (1.04–2.29, 0.03)
RT only	1.76 (1.19–2.60, 0.004)	0.93 (0.61–1.43, 0.74)
Chemo/RT	4.16 (3.19–5.43, <0.001)	1.02 (0.72–1.45, 0.90)

grade, and hyperlipidemia ($p < 0.05$) (Table 3). Any additional treatment (chemotherapy, radiation therapy, or both) was associated with increased hazard of death in multivariable analysis of women with endometrioid cancers. BMI was not significantly associated with DSS after controlling for the aforementioned variables (Wald $p = 0.15$).

In the subgroup of women with non-endometrioid histology, survival curves were significantly different between BMI categories as women with higher BMI having improved survival (log rank $p < 0.003$, Supplementary Fig. 2). In this cohort, there were significant differences in age, race, hypertension, and diabetes associated with obesity categories ($p < 0.05$). Unlike the endometrioid patients, stage, grade, metformin use and use of adjuvant therapy were not associated with obesity. In univariable Cox regression analysis, age at diagnosis, BMI, stage, hypertension, diabetes, hyperlipidemia, adjuvant therapy, and metformin and statin use were associated with disease-specific survival ($p < 0.05$). In multivariable Cox regression analysis of women with non-endometrioid cancers, younger age at diagnosis, lower stage, treatment utilizing both chemotherapy and radiation, and statin use remained independently associated with decreased hazard of death ($p < 0.05$). BMI was not independently associated with survival after controlling for these factors (Wald $p = 0.11$). However, in comparison of patients with non-endometrioid cancers and Class 2 obesity to normal weighted patients with Class 2 obesity there was an improved survival for the obese group (HR 0.59; 95% CI 0.37–0.94, $p = 0.03$).

As stage was such a strong predictor of survival for women with non-endometrioid cancers (Stage 3, HR 7.1; 95% CI 4.9), the models were further stratified by this factor. In women with non-endometrioid histology and extra-uterine disease at presentation (Stage 3 and 4), age was no longer significantly associated with DSS. The only remaining factors independently associated with a decreased hazard of DSS were treatment with both chemotherapy and radiation and statin use (Table 4). Although BMI overall was non-significant, the 2 highest BMI groups (BMI 35–39.9 and >40) had a decreased hazard of death compared to women with a normal BMI ($p = 0.01$ and $p = 0.08$, respectively).

In our study, the sub-cohort most likely to be effected by high risk features was identified to be endometrioid type lesions, clinically confined to the uterus (Stage I). The high risk features that were evaluated included depth of invasion by percentage myometrial invasion, lymph vascular space invasion and tumor grade. Of 998 women identified to have endometrioid type lesions confined to the uterus, data were evaluable for 934 (94%). In univariable analysis, for women with Stage 1 endometrioid histology, body mass index was associated with depth

Table 3
Univariable and multivariable Cox proportional hazards regression models stratified by histology.

Variable	Endometrioid histology		Non-endometrioid histology	
	Univariable Hazard Ratio (95% CI, *p*-value)	Multivariable Hazard Ratio (95% CI, *p*-value)	Univariable Hazard Ratio (95% CI, *p*-value)	Multivariable Hazard Ratio (95% CI, *p*-value)
Age (years)	1.06 (1.05–1.08, <0.001)	1.06 (1.05–1.08, <0.001)	1.03 (1.01–1.04, <0.001)	1.02 (1.01–1.04, 0.001)
BMI (kg/m^2)	Overall Wald $p = 0.02$	Overall Wald $p = 0.15$	Overall Wald $p = 0.002$	Overall Wald $p = 0.11$
Normal (18.5–24.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25–29.9)	0.68 (0.44–1.06, 0.09)	1.16 (0.69–1.96, 0.57)	0.69 (0.51–0.94, 0.01)	0.77 (0.56–1.09, 0.14)
Obese (30–34.9)	0.54 (0.34–0.83 (0.006)	1.08 (0.64–1.83, 0.78)	0.73 (0.54–0.98, 0.04)	0.93 (0.66–1.30, 0.66)
Obese (35–39.9)	0.48 (0.29–0.80, 0.004)	0.64 (0.35–1.17, 0.14)	0.48 (0.31–0.73, 0.001)	0.59 (0.37–0.94, 0.03)
Morbid Obese (>40)	0.52 (0.33–0.82, 0.005)	1.19 (0.69–2.07, 0.53)	0.52 (0.34–0.79, 0.002)	0.68 (0.43–1.09, 0.11)
Ethnicity	Overall Wald $p = 0.49$		Overall Wald $p = 0.26$	
White/Caucasian	1.00 (reference)		1.00 (reference)	
Black – non Hispanic	1.01 (0.71–1.43, 0.96)		0.89 (0.68–1.17, 0.39)	
Hispanic	0.87 (0.61–1.22, 0.41)		0.78 (0.56–1.10, 0.15)	
Asian	0.37 (0.09–1.51, 0.17)		0.76 (0.31–1.87, 0.55)	
Other	0.84 (0.37–1.93, 0.69)		0.46 (0.20–1.07, 0.07)	
Stage	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$
1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.90 (1.17–3.08, 0.009)	1.52 (0.86–2.69, 0.15)	1.90 (1.22–2.97, 0.005)	1.72 (1.07–2.78, 0.03)
3	2.69 (1.68–4.31, <0.001)	1.50 (0.84–2.69, 0.18)	3.01 (2.19–4.12, <0.001)	3.21 (2.27–4.54, <0.001)
4	8.47 (5.03–14.28, <0.001)	4.69 (2.34–9.40, <0.001)	7.92 (5.90–10.63, <0.001)	7.10 (4.91–10.28, <0.001)
Unstaged**	6.22 (3.64–10.63, <0.001)	4.83 (2.76–8.44, <0.001)	9.24 (5.66–15.09, <0.001)	7.39 (4.33–12.59, <0.001)
Grade	Overall Wald $p < 0.001$	Overall Wald $p = 0.02$	–	–
1	1.00 (reference)	1.00 (reference)		
2	1.85 (1.35–2.54, <0.001)	1.17 (0.81–1.69, 0.39)		
3	2.94 (2.04–4.25, <0.001)	1.91 (1.22–2.98, 0.005)		
Hypertension				
No	1.00 (reference)		1.00 (reference)	
Yes	1.20 (0.89–1.61, 0.24)		0.84 (0.66–1.06, 0.15)	
Diabetes				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.32 (0.98–1.76, 0.06)	1.59 (1.13–2.24, 0.008)	0.75 (0.58–0.97, 0.03)	1.24 (0.88–1.74, 0.22)
Hyperlipidemia				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Yes	0.76 (0.56–1.01, 0.06)	0.61 (0.44–0.86, 0.004)	0.55 (0.43–0.71, <0.001)	
Statin use				
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Yes	0.93 (0.68–1.27, 0.65)		0.59 (0.45–0.78, <0.001)	0.62 (0.47–0.82, 0.001)
ASA use				
No	1.00 (reference)		1.00 (reference)	
Yes	1.14 (0.80–1.63, 0.47)		0.88 (0.66–1.16, 0.36)	
Metformin				
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Yes	0.79 (0.51–1.22, 0.28)		0.52 (0.36–0.76, 0.001)	0.65 (0.40–1.05, 0.08)
Beta blocker				
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	
Yes	1.75 (1.29–2.38, <0.001)	1.20 (0.86–1.66, 0.29)	1.09 (0.85–1.39, 0.50)	
Treatment	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$	Overall Wald $p < 0.001$	Overall Wald $p = 0.007$
No chemo/No RT	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Chemo only	3.59 (2.18–5.94, <0.001)	3.87 (2.13–7.04, <0.001)	1.77 (1.29–2.43, <0.001)	0.95 (0.64–1.42, 0.80)
RT only	1.77 (1.23–2.54, 0.002)	1.01 (0.65–1.56, 0.98)	0.71 (0.44–1.12, 0.14)	0.82 (0.49–1.34, 0.42)
Both chemo/RT	4.28 (2.95–6.19, <0.001)	2.84 (1.73–4.65, <0.001)	0.62 (0.46–0.84, 0.002)	0.61 (0.43–0.86, 0.005)

of invasion, grade, and lymph vascular invasion ($p < 0.05$) Higher body mass index was associated with lower grade, less invasion, and absence of lymph vascular space invasion. After controlling for all three high risk factors, only grade was independently associated with body mass index ($p < 0.05$), with higher body mass index exhibiting Grade 1 disease. Race was also independently associated with body mass index in this cohort of women with Stage I endometrioid histology, with black and hispanic women having on average higher body mass index than white women. Race, however, did not alter the associations of high-risk variables with obesity. There was no association seen for estrogen or progesterone receptor positivity and body mass index. This association was not influenced by race. Only 21 (2%) of 934 patients had Lynch testing, and therefore no meaningful associations to obesity or race could be concluded.

In our diverse population there were differences in histologies associated with race. Black women represented only 24% of the women with endometrioid histologies and 56% of the women with non-endometrioid histologies. In the overall cohort, endometrioid only and non-endometrioid histologies, there was a significant association with race and body mass index. Women of black race were more likely to have body mass indices in the highest categories (Table 1). For women with endometrioid type cancer 75% of black women had body mass indices over 30 mg/kg^2 in comparison to 64% of white women. For non-endometrioid cancers, 62% of black women had body mass indices over 30 kg/m^2 as compared to 44% of white women. When data for the entire cohort were analyzed in a univariable fashion black race was significantly associated with increased hazard of death, (HR 1.95, 95% CI 1.53–2.5 $p < 0.001$), but when other variables were included in multivariable analysis black race was not shown to be associated with survival (HR 0.99, 95% CI 0.75–1.31, $p = 0.96$).(Table 2) Similarly there was no increased hazard for death associated with race when histologies of endometrioid versus non-endometrioid were considered separately. (Table 3) There was no alteration of the association of high risk factors of depth of invasion, tumor grade and lymph vascular space invasion associated with race for early stage endometrioid cancers confined to the uterus.

Table 4
Cox regression analysis limited to non-endometrioid cancer stratified stage.

Variable	Type 2 Endometrial Cancers Stage 1/2		Type 2 Endometrial Cancers Stage 3/4	
	Univariable Hazard Ratio (95% CI, *p*-value)	Multivariable Hazard Ratio (95% CI, *p*-value)	Univariable Hazard Ratio (95% CI, *p*-value)	Multivariable Hazard Ratio (95% CI, *p*-value)
Age (years)	1.03 (1.00–1.05, 0.07)		1.01 (0.99–1.03, 0.28)	1.00 (0.99–1.02, 0.77)
BMI (kg/m^2)	Overall Wald $p = 0.38$		Overall Wald $p = 0.004$	Overall Wald $p = 0.11$
Normal (18.5–24.9)	1.00 (reference)		1.00 (reference)	1.00 (reference)
Overweight (25–29.9)	0.84 (0.45–1.56, 0.58)		0.56 (0.38–0.84, 0.005)	0.71 (0.46–1.10, 0.12)
Obese (30–34.9)	0.66 (0.35–1.26, 0.21)		0.67 (0.45–0.98, 0.04)	0.81 (0.53–1.24, 0.33)
Obese (35–39.9)	0.43 (0.17–1.09, 0.08)		0.38 (0.22–0.67, 0.001)	0.48 (0.26–0.88, 0.01)
Morbid Obese (>40)	0.73 (0.33–1.60, 0.43)		0.47 (0.26–0.85, 0.01)	0.58 (0.31–1.07, 0.08)
Ethnicity	Overall Wald $p = 0.14$		Overall Wald $p = 0.45$	
White/Caucasian	1.00 (reference)		1.00 (reference)	
Black – non Hispanic	0.90 (0.52–1.56, 0.70)		0.87 (0.61–1.24, 0.43)	
Hispanic	0.79 (0.40–1.53, 0.48)		0.77 (0.49–1.20, 0.25)	
Asian	0.67 (0.09–5.00, 0.69)		1.26 (0.45–3.53, 0.65)	
Other	–		0.47 (0.17–1.31, 0.15)	
Hypertension				
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Yes	0.77 (0.48–1.26, 0.30)		0.70 (0.52–0.96, 0.03)	1.00 (0.70–1.42, 0.99)
Diabetes				
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Yes	1.08 (0.67–1.74, 0.75)		0.57 (0.39–0.83, 0.004)	0.70 (0.46–1.07, 0.10)
Hyperlipidemia				
No	1.00 (reference)		1.00 (reference)	–
Yes	0.70 (0.44–1.12, 0.14)		0.50 (0.35–0.71, <0.001)	
Statin use				
No	1.00 (reference)		1.00 (reference)	1.00 (reference)
Yes	0.66 (0.39–1.14, 0.14)		0.55 (0.37–0.80, 0.002)	0.59 (0.39–0.89, 0.01)
ASA use				
No	1.00 (reference)		1.00 (reference)	
Yes	1.08 (0.63–1.86, 0.77)		0.77 (0.51–1.15, 0.20)	
Metformin				
No	1.00 (reference)		1.00 (reference)	
Yes	0.64 (0.32–1.24, 0.19)		0.64 (0.36–1.12, 0.12)	
Beta blocker				
No	1.00 (reference)		1.00 (reference)	
Yes	1.18 (0.71–1.94, 0.53)		1.17 (0.83–1.64, 0.36)	
Treatment	Overall Wald $p = 0.17$		Overall Wald $p < 0.001$	Overall Wald $p < 0.001$
No chemo/No RT	1.00 (reference)		1.00 (reference)	1.00 (reference)
Chemo only	2.00 (0.94–4.26, 0.07)		0.85 (0.56–1.27, 0.42)	0.98 (0.62–1.55, 0.93)
RT only	1.23 (0.54–2.80, 0.63)		0.33 (0.10–1.07, 0.07)	0.34 (0.10–1.14, 0.08)
Both chemo/RT	0.97 (0.52–1.82, 0.94)		0.34 (0.23–0.52, <0.001)	0.43 (0.27–0.68, <0.001)

4. Discussion

Age at diagnosis was younger for patients in the highest BMI categories for the entire cohort and subgroups of endometrioid and non-endometrioid cancers. In the entire cohort and subgroups of endometrioid and non-endometrioid histologies this relationship was linear. In multivariable analysis obesity was not associated with overall or disease specific survival, but factors of age, stage, grade, statin use, anti-hyperglycemic, and adjuvant therapy remained significant. However, in a subgroup of non-endometrioid patients, with Stage 3 and 4 disease, age was no longer associated with survival and patient in the obese category had decreased hazard of death. In our dataset, obese patients did not have a higher overall hazard of death from co-morbidities frequently associated with obesity such as cardiovascular death. Additionally, when the presence of high-risk features was evaluated for association with obesity only Grade 1 disease was associated with higher BMI, which may suggest metabolic pathways important in pathogenesis. These data, in particular the impact of statin and anti-hyperglycemic medications, suggest the potential importance of anti-inflammatory and metabolic pathways as well as estrogen pathways in endometrial cancer, whereby obese women have high levels of endogenous estrogen due to the conversion of androsteedione to estrone and the aromatizaion of androgens to estradiol in peripheral adipose tissue.

The findings from our study are in sharp contrast to those reported by the two cooperative group trials that reported decrease in survival associated with increased BMI [12,15]. The cause for this difference is unclear. In the analysis by Modesitt et al. of 5 Gynecologic Oncology Group trial participants who received doxorubicin and cisplatin, the authors suggest that dose capping may have been responsible for decreased survival (approximately 46% of patients with body surface area greater than 2 m^2 had capping of doxorubicin, cisplatin or both). However, in that analysis dose capping was not associated with worse prognosis (HR 1.46, $p = 0.13$) [12]. In comparison to the study by Billingsley et al. that was restricted to Type II cancers and found no association with BMI and mortality for Type II endometrial cancer survivors, we found a protective effect in obese patients with non-endometrioid histology and Stage 3 and 4 disease, which may be explained by an increased ability to tolerate adjuvant therapy or better pretreatment performance index. Our study population differed greatly from the patients enrolled in the Gynecologic Oncology Group studies in that only 30% of patients in our population self-identified as white and non-Hispanic. Only 30% of patients in the Gynecologic Oncology Group study identified as non-white, Hispanic, or other. Despite the finding that obesity was associated with improved survival in the subgroup of women with non-endometrioid cancers, and that more black women in our study were in higher body mass index categories then women of other races there was not an association between improved or worsened survival for black women in multivariable modeling in our study. Additionally, in our study we accounted for metformin and statin, which were significantly associated with decreased hazard of death and were not included in the previous studies.

Our data are similar to those of Jeong et al. in that obesity appeared protective until multivariable accounting for confounding factors, most notably age at diagnosis [9]. Mustedt et al. reported that obesity did not adversely affect survival as accounted for by younger age and less advanced disease at time of diagnosis [7]. Similarly, Anderson et al. concluded that obesity positively affects survival from endometrial cancer by the diagnosis of less aggressive disease in obese patients [6]. Obesity has a role in carcinogenesis at an earlier age which must be accounted for in studies of the relationship of obesity to cancer survival.

Shortcomings of our study include the data abstraction from retrospective chart review.

Additionally, patients' weight loss or weight gain could not be accounted for as BMI was recorded at time of diagnosis and not followed longitudinally through survivorship. Medication utilization was subject to bias as presented in the medical record and adherence through pharmacy records was not assessed, and chemotherapy dosing was at the discretion of the attending physicians and not subject to universal capping.

In conclusion, the main effect of high BMI in both endometrioid and non-endometrioid was diagnosis of endometrial cancer at a younger age. These data also suggest that important factors associated with endometrial cancer survival in both endometrioid and non-endometrioid subgroups may be medications associated with metabolic diseases including metformin and statins. Future research is needed to understand if obese women with endometrial cancer may benefit from antihyperlipidemic or antihyperglycemic therapy. It is unclear as to why our data differ from patients enrolled in Gynecologic Oncology Group cooperative group trials. While the most striking difference between our population and the women who participated in the Gynecologic Oncology Group cooperative group trial was race, race was not an independent factor associated with survival in our cohort, and it was not independently associated with high risk features. Further investigation of genetic composition of tumors and the role of metabolic pathways may help us to better understand the relationship of obesity and race in endometrial cancers. Additionally, and the role of chemotherapy dose capping is also undetermined in this population and in obese cancer patients.

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Authors have no conflicts of interest to report

All authors contributed equally to the research and writing of the manuscript. Dr. Van Arsdale provided statistics and contributed significantly to the methods, results and discussion sections. Dr. Miller provided significant contribution to the abstract, introduction, discussion and results section. Dr. Kuo provided significant contribution to the discussion and provided significant editing. Dr. Isani provided significant contribution to the introduction and extensive edits. Ms. Sanchez provided the data gathering and aided with long-term follow up results. Dr. Nevadunsky served as senior author and contributed significantly to the entire manuscript.

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