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Histopathologic differences account for racial disparity in uterine cancer survival

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Abstract

Objective—The incidence for uterine cancers has been reported to be higher among white women, whereas mortality is higher among black women. Reasons for the higher mortality among black women are not completely understood. The aim of our study is to examine the relationship between race/ethnicity, histopathologic subtype, and survival in uterine cancer.

Methods—We abstracted socio-demographic, treatment, and survival data for all women who were diagnosed with uterine cancer at Montefiore Medical Center from January 1999 through December 2009. Pathology records were reviewed.

Results—984 patients were identified. Racial/ethnic distribution was 382 (39%) white, 308 (31%) black, 232 (24%) Hispanic, and 62 (6.3%) other races, mixed, or unknown. 592 (60%) patients had endometrioid histology. Blacks were much more likely than whites to have non-endometrioid histologies ($p<0.001$), including papillary serous, carcinosarcoma, and leiomyosarcoma. Blacks and Hispanics were at least as likely as whites to receive either chemotherapy or radiation therapy. The hazard ratio for death for black versus white patients was 1.94 ($p<0.001$) when all histological subtypes were included. The hazard ratio for Hispanics for death was 1.2 ($p=0.32$) compared to whites. However, when patients were divided into endometrioid and non-endometrioid histological subtypes, there was no significant difference in survival by race/ethnicity.

Conclusion—Black patients with uterine cancer are much more likely to die and are much more likely to have non-endometrioid histologies than white patients. There are no differences in survival among white, black, or Hispanic women with uterine cancer, after control for histological subtype.

Keywords

Uterine cancer; Racial; Disparity; Histology; Survival

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Introduction

Uterine cancer is the most prevalent reproductive cancer among women, with over 40,000 new cases diagnosed in the United States each year [1]. Racial disparities in survival have been described for women treated for cancers of the uterine corpus. In the United States incidence rates for malignant tumors of the uterine corpus are lower among blacks than among whites, whereas mortality rates are higher among blacks [2]. In a literature review of 14 different cancers, the most striking disparity for mortality between whites and blacks was for cancer of the uterine corpus [3]. Reasons for the higher level of mortality among blacks are debated and not completely understood. Poorly-differentiated and aggressive non-endometrioid histologic types are more common in black women [2,4]. Many studies to date cite less favorable outcomes for blacks in both the usual type of endometrioid adenocarcinoma as well as for the more aggressive non-endometrioid tumors even after controlling for stage and grade of disease [2,5,6].

Montefiore Medical Center serves the health care needs of the Bronx, a county of almost 1.4 million people and with a high proportion of black and Hispanic women. The Bronx Hispanic population largely originates from the Caribbean, particularly the Dominican Republic and Puerto Rico. The objective of our study was to evaluate the relationship of race/ethnicity (white, black, Hispanic) to survival in uterine cancer and to explore the association of histology to race and survival.

Materials and methods

Institutional Review Board approval was obtained for a retrospective review of all patients who received care at Montefiore Medical Center for cancer of the uterine corpus, from January 1, 1999 to December 31, 2009. No patients were excluded in the initial analysis. Age was determined from the date of diagnosis. Race/ethnicity was determined by review of all medical records. In most patients the race/ethnicity was listed in the registration documentation, which is obtained by direct query of the patient by the registration administrator. Further analysis was limited to patients designated as white, black, or Hispanic, and all other patients were excluded. Stage was determined by the 1988 International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria [7], when complete surgical staging was performed. In patients without complete surgical staging, a FIGO stage was assigned based on review of all clinical findings. If there was insufficient information, then the patient's cancer was described as unstaged. Reasons for lack of adequate staging information included medical co-morbidities precluding surgical staging and patients desiring fertility preservation. Body mass index (BMI) was calculated by weight in kilograms divided by the square of the height in meters (kg/m^2).

All pathology reports were reviewed and each cancer was designated as one of the following types: endometrioid, papillary serous (UPSC), carcinosarcoma, clear cell, adenosarcoma, leiomyosarcoma, undifferentiated endometrial sarcoma, endometrial stromal sarcoma, and poorly-differentiated endometrial cancer. Cancers were designated as UPSC if any fraction of the cancer was papillary serous. The designation of poorly-differentiated endometrial cancer was reserved for those high-grade cancers in which histologic type could not be determined. Undifferentiated endometrial sarcoma and endometrial stromal sarcoma are the most recent terms for what was previously designated as high-grade endometrial stromal sarcoma and low-grade endometrial stromal sarcoma, respectively.

Endometrioid cancers were designated as grade 1, 2, or 3. All UPSC, carcinosarcomas, leiomyosarcomas, clear cell carcinomas, poorly-differentiated carcinomas, and undifferentiated endometrial sarcomas were designated as grade 3. Endometrial stromal

sarcomas were designated as grade 1. “Not applicable” was the designation for adenosarcoma as this was not assigned a grade.

Survival was calculated from the date of diagnosis to date of death from any cause. Date of death was obtained by review of medical records or by review of the Social Security Death Index in 10/2010.

Differences between whites, blacks, and Hispanics in the distributions of histology, stage, and grade were tested by the chi-square method or, when appropriate, the Fisher's exact test. Two sample t-test was used to compare the mean differences of BMI and age between endometrioid and non-endometrioid patients. Survival curves were created using the Kaplan–Meier method, and differences were measured using the Log-rank test. Cox proportional hazard modeling was used to assess the impact of histologic type on survival. The Statistical Analysis Software (SAS) package was used, version 9.1.2.

Results

A total of 984 total patients were evaluated. 382 (39%) were white, 308 (31%) were black, and 232 (23.5%) were Hispanic. The remaining 62 (6.3%) patients were of mixed, unknown, Asian, Indian, or other races.

Mean age of all patients was 64 years. Mean age for blacks and whites was 65, and for Hispanics was 61. Including all races/ethnicities, the mean age of women with non-endometrioid tumors was greater than that for women with endometrioid tumors (67 vs. 62 years, p -value<0.001).

Data was available to calculate BMI for 91% of patients. Mean BMI for whites and blacks was 33, and for Hispanics was 32. For all races/ethnicities, the mean BMI of women with non-endometrioid tumors was less than that for endometrioid tumors (30 vs. 34, p -value<0.001).

When analyzing only endometrioid tumors, the distribution of stages was similar for whites, blacks, and Hispanics (Table 1). For non-endometrioid tumors, blacks as compared to whites were somewhat more likely to have stage 3 disease (25% vs. 16%, p =0.14) and somewhat less likely to have stage 1 disease (41% vs 53%, p =0.056) (Table 2). These differences were not statistically significant.

When only endometrioid tumors were examined, blacks were less likely to have grade 1 cancers than whites (50% vs. 67%, p -value=0.0013) and more likely to have grade 3 tumors (23% vs. 12%, p -value=0.0068). Hispanics with endometrioid tumors had a similar grade distribution as whites with 67% with grade 1 tumors for both whites and Hispanics.

Black women had a much higher proportion of non-endometrioid cancers than white women (63% vs. 26%, p <0.001) and Hispanic women had a moderately higher proportion as compared to white women (35% vs. 26%, p <0.02) (Table 3). The histologic types with poor prognosis made up a larger fraction of cancers in blacks than in whites. This included UPSC (35.7% vs. 13.9%, p <0.001), carcinosarcoma (14.9% vs. 7.1%, p =0.001), leiomyosarcoma (5.2% vs. 1.0%, p =0.02), and undifferentiated endometrial sarcoma (1.9% vs. 0.3%, p <0.05). Clear cell and poorly-differentiated types also made up a greater proportion of cancers in blacks, but these were not statistically significant findings. UPSC was strikingly more frequent in our cohort than previously reported. Among Hispanic women, there was a moderately higher fraction of non-endometrioid cancers, but no statistically significant increase in any one histologic type.

Review of treatments received by these patients at Montefiore Medical Center revealed that 87% of all patients underwent full surgical staging. 14% of whites, 8% of blacks, and 15% of Hispanics did not undergo full surgical staging. Either radiation therapy or chemotherapy was provided to a larger proportion of blacks and Hispanics than whites (Table 4).

For all cancers, Kaplan–Meier survival curves were similar for whites and Hispanics, but survival was significantly worse for blacks (Fig. 1). The hazard ratio for death was 1.94 ($p<0.0001$) for blacks compared to whites. The hazard ratio for Hispanics for death was 1.2 ($p=0.32$) compared to whites, a difference which is not statistically significant.

A Cox proportional hazard model was created in which histology was the only variable and survival was compared between whites, blacks and Hispanics. We did not control for stage and grade as these variables were strongly dependent on histology. In this Cox model, when histology was divided into endometrioid and non-endometrioid types, race does not impact survival. When controlled for histology, the hazard ratio for death by blacks compared to whites is 1.12 (95% Confidence Interval, 0.84–1.48) and the hazard ratio for Hispanics is 0.93 (95% Confidence Interval, 0.67–1.29).

Discussion

Our study presents the largest number of black and Hispanic women with uterine cancer from a single institution. In this study, we find that black women with uterine cancer have a strikingly poorer survival than whites or Hispanics. Black women with uterine cancer are much more likely to have non-endometrioid histology and this appears to be sufficient to explain the differences in survival at our institution. Statistically significant differences between blacks and whites were noted for the proportions of UPSC, carcinosarcoma, and leiomyosarcoma, and undifferentiated endometrial sarcoma.

The reason for the increased fraction of non-endometrioid cancer in black women is unknown. The proportion of patients with UPSC in our study is much higher than that noted in any prior study. A possible contributing factor may be the increasing recognition by pathologists of the UPSC diagnosis since the first description of this entity in 1982 [8]. Our study reviews patients over a later period of time as compared to previously published studies, and there may be trends to increasing diagnosis of the papillary serous type. Wright et al. [6] analyzed the Surveillance, Epidemiology, and End Results (SEER) program database from 1988 to 2004 and found that the incidence of UPSC and clear cell cancers increased over time. For white women, UPSC and clear cell diagnosis increased from 4.6% in 1988–1993 to 6.4% in 1999–2004. For blacks, UPSC and clear cell increased from 9.9% in 1988–1993 to 15.1% in 1999–2004. Another analysis of the SEER database [9] from 1988 to 2001 also showed a trend over time of increasing proportion of high-risk histologic types including UPSC and sarcomas. Those authors also noted that the proportion of grade 3 tumors increased over time. It is unknown if this trend is due to a decrease in incidence of low-risk endometrioid cancer, or to an increase in high-risk cancers, or both. Over that time period there was a decrease in death rate for white women, with an increase in death rate among black women. It is possible that the same trends are present for women in the Bronx. Our study involves women from a more recent time span and the trends may have continued to accelerate.

Another possible reason for a higher fraction of UPSC in our study is the designation in our study of a cancer as UPSC even when there is a mixture of papillary serous with other histologic types and even if the papillary serous component comprises a minor fraction. Studies in the past may not have made this designation. As noted by some investigators, UPSC is often mixed with other histologic types [8,10,11]. In a study of 206 patients with

stages I and II UPSC, 46% of cases contained a mixture with other histologic types, and the authors noted that cancers with any fraction of UPSC, with a minimum of 5%, had a similar risk of recurrence as pure UPSC [12]. Also a report by Sherman et al. showed that relapse rates were similar whether the UPSC was pure or mixed [10]. Goff et al. reported that a mixed or pure histology for UPSC did not predict extrauterine disease [11].

Our study also found the proportion of carcinosarcoma and leiomyosarcoma to be strikingly higher in blacks than in either whites or Hispanics. A prior study of the SEER database from 1989 to 1999 similarly showed a much higher incidence of both carcinosarcoma and leiomyosarcoma in blacks than in whites [13].

In our study, Cox regression analysis shows that the poorer survival for blacks with uterine cancer can be almost entirely explained by a higher fraction of non-endometrioid histologic types. There was no survival disparity between blacks and whites for the endometrioid type, nor for non-endometrioid cancers.

In contrast to our results, studies based on the SEER database have found disparity in survival between blacks and whites both for endometrioid and non-endometrioid cancers [2,6]. Some authors in the past have suggested that part of the explanation for racial differences in survival may be due to disparities in treatment or access to care.

Our findings are consistent with those of Matthews et al. [14] who found that race was not an independent risk factor for survival. Their study was based on a single institution in Brooklyn from 1982 through 1995. They found that in blacks, 80% of tumors are endometrioid and 16% were UPSC. They found only stage and histologic type to be significant risk factors for survival. Also, a prior study of patients with UPSC, from two large hospitals in Detroit, found that survival is the same for blacks and whites [15]. These authors suggested that survival differences might be diminished in single institution studies where there is more uniform management of patients. Our study is also based on a single institution where there may be an advantage in the greater consistency in pathologic diagnosis and greater uniformity in management of these patients.

We would conclude that, at our institution, cancer biology is the most important determinant of the differences in outcomes for uterine cancer in black versus white women. Disparities in care do not appear to explain the differences at our institution, but may be important factors in other settings. The nature of the biological factors is unknown and the relative contributions of environmental or genetic influences to cancer incidence in blacks and whites remain to be determined. A full understanding of the genetic and environmental factors would explain both a higher incidence of good prognosis endometrioid tumors in whites as well as a higher incidence of aggressive non-endometrioid tumors in blacks.

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HIGHLIGHTS

We study the relationship of histology and race/ethnicity to survival in uterine cancer patients at a single institution.

Blacks are much more likely to have non-endometrioid uterine cancers, including uterine papillary serous, carcinosarcoma, and leiomyosarcoma.

Risk of death is much higher with blacks than whites, largely because of differences in the distribution of histologic types.

Fig. 1.
Survival of uterine cancer by race/ethnicity.

Table 1

Distribution of age, BMI, grade, and stage of patients with endometrioid tumors by race/ethnicity.

	White (n=283)		Black (n=113)		Hispanic (n=150)	
Mean age in years	64		63		59	
Mean BMI	33		36		34	
<i>Stage</i>						
1	236	83%	90	80%	122	81%
2	20	7%	11	10%	7	5%
3	18	6%	6	5%	11	7%
4	4	1%	5	4%	3	2%
Unstaged	5	2%	1	1%	7	5%
<i>Grade</i>						
1	191	67%	56	50%	<i>p</i> =0.0013	100 67%
2	60	21%	31	27%		38 25%
3	33	12%	26	23%	<i>p</i> =0.0068	12 8%

Table 2

Distribution of age, BMI, and stage of patients with non-endometrioid tumors by race/ethnicity.

	White (n=98)		Black (n=195)			Hispanic (n=82)	
Mean age in years	69		67			66	
Mean BMI	30		31			29	
<i>Stage</i>							
1	52	53%	79	41%	$p=0.056$	41	50%
2	7	7%	18	9%		7	9%
3	16	16%	48	25%	$p=0.14$	14	17%
4	22	22%	43	22%		17	21%
Unstaged	1	1%	7	4%		3	5%

Table 3

Distribution of uterine cancer histology by race/ethnicity, 1994–2009.

	White (n=382)		Black (n=308)			Hispanic (n=232)		
Endometrioid	284	74.3%	113	36.7%	$p<.001$	150	64.7%	$p<.02$
UPSC	53	13.9%	110	35.7%	$p<.001$	39	16.8%	
Carcinosarcoma	27	7.1%	46	14.9%	$p=.001$	15	6.5%	
Leiomyosarcoma	4	1.0%	16	5.2%	$p=.002$	7	3.0%	
Clear cell	6	1.6%	8	2.6%		6	2.6%	
Poorly-differentiated	3	0.8%	6	1.9%		5	2.2%	
Undifferentiated endometrial sarcoma	1	0.3%	6	1.9%	$p<.05$	2	0.9%	
Endometrial stromal sarcoma	3	0.8%	2	0.6%		5	2.2%	
Adenosarcoma	1	0.3%	1	0.3%		3	1.3%	

Table 4

Treatment by race/ethnicity.

	White		Black		Hispanic	
Endometrioid	(n=283)		(n=113)		(n=150)	
Chemotherapy	12	4%	11	10%	12	8%
Radiation	63	22%	36	32%	36	24%
Nonendometrioid	(n=98)		(n=195)		(n=82)	
Chemotherapy	39	40%	98	50%	43	52%
Radiation	47	48%	110	56%	51	62%