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Racial Disparities in Survival among Women with Endometrial Cancer in an Equal Access System

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Abstract

Objective: The mortality rate for Black women with endometrial cancer (EC) is double that of White women, although the incidence rate is lower among Black women. Unequal access to care may contribute to this racial disparity. This study aimed to assess whether survival varied between non-Hispanic Black (NHB) and non-Hispanic White (NHW) women with EC in the Military Health System (MHS) which provides equal access care to its beneficiaries despite racial/ethnic background.

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Conflict of Interest

Dr. Casablanca reports other from Pfizer, other from Regeneron, outside the submitted work.

Methods: The study was conducted using data from the U.S. Department of Defense's (DoD) Automated Central Tumor Registry (ACTUR). Study subjects included NHB and NHW women with histologically confirmed and surgically managed EC diagnosed between 1988 and 2013. The study outcome was all-cause death. Overall survival between NHB and NHW women was compared using multivariable Cox modeling.

Results: The study included 144 NHB and 1,439 NHW women with EC. Kaplan-Meier curves showed NHB women had worse survival than NHW women (log-rank P<0.0001). The disparity in survival between NHB and NHW women persisted after adjusting for age, diagnosis period, tumor stage, tumor histology/grade, and adjuvant treatment (HR=1.64, 95% CI=1.19 to 2.27). Multivariable analyses stratified by tumor features or treatment showed that the racial disparity was confined to women with low-risk features (stage I/II disease or low-grade EC) or no adjuvant treatment.

Conclusion: There were racial differences in overall survival between NHB and NHW women with EC in the MHS equal access healthcare system, suggesting that factors other than access to care may be related to this racial disparity.

Introduction

Cancer of the uterine corpus is the most common gynecological malignancy diagnosed among women in the United States, with 65,620 estimated new cases and 12,590 deaths in 2020 (1). Research has found that the mortality rate of endometrial cancer among Black women is nearly double that among White women, although the incidence is higher among White women (2). These racial disparities may be related to later tumor stage at diagnosis, higher tumor grade, and more aggressive histology types among Black women (3–7). However, some studies showed that survival remains less favorable among Black women than White women with tumor of similar stage, grade, and histology (6–9).

While racial disparities in endometrial cancer survival are likely multifactorial, inequities in access to medical care and insurance between racial groups in the U.S. general population may be important factors (10, 11). In the United States, Black women are less likely to have medical insurance than White women (11). Lack of health insurance or access to care may delay the detection of cancer and negatively affect the timing and quality of cancer treatments, which may result in worse clinical outcomes and premature death. Prior research has reported that compared to White women, Black women were more likely to present with later stage tumors, aggressive histology, and poor tumor grade; were less likely to receive hysterectomies; and had shorter survival (8).

Conducting research within an equal healthcare access system may help elucidate the factors that contribute to the racial disparities. If racial disparities are not observed in an equal access system, it suggests that unequal access to healthcare may play a significant role in observed disparities in the general population. On the other hand, an observed racial difference in an equal access system may suggest the potential effects of factors other than access to care. In early studies in the Henry Ford Healthcare System, a managed health care organization that provides care to all its members, Black women with endometrial cancer had worse survival than White women, but the racial difference became non-significant after

adjustment for age and tumor variables (12) or tumor stage and other pathologic features (13).

The United States Department of Defense's (DoD's) Military Health System (MHS) provides its beneficiaries with equal access to care regardless of race, ethnicity or socioeconomic factors and is therefore an important resource for investigating racial disparities in cancer health outcomes. In a previous study based on the DoD cancer registry data, Kost et al. showed that Black women diagnosed with endometrial cancer from 1988 to 1995 had worse survival compared to White women, but the difference disappeared after adjustment for tumor stage (14), which was later among Black women than White women in the population (15). The purpose of this study was to investigate whether there were racial differences in survival among NHB and NHW women diagnosed with endometrial cancer of the uterine corpus in the DoD cancer registry data, using the data from a longer period (1988 to 2013) and adjusting for not only tumor stage but also adjuvant therapy.

Methods

Data Source

This study was conducted using data from the DoD's Automated Central Tumor Registry (ACTUR). The ACTUR was initiated in 1986 for the collection of information on all DoD beneficiaries including active-duty members, retirees and their dependents who are diagnosed with cancer or receive cancer treatment at military treatment facilities. Local registrars review and verify all cases reported to ACTUR and follow all cases until death. The ACTUR data contain information on age at diagnosis, sex, race, ethnicity, primary site, tumor stage, histology, diagnosis date, diagnostic confirmation, cancer treatment, recurrence, last contact date, death date, and vital status. The use of the data for research was approved by the institutional review boards of Walter Reed National Military Medical Center and the National Institutes of Health.

Study Subjects

Non-Hispanic White and non-Hispanic Black women histologically diagnosed with endometrial cancer of the uterine corpus between 1988 and 2013 were eligible for the study. Endometrial cancer was defined using International Classification for Oncology (ICD-O) topography codes (C540-C543 and C548-C549) and histologic codes (see appendix) (16–17). Histologic types were dichotomized into endometrioid or non-endometrioid groups. Endometrioid cancers were divided into low grade, high grade, and ungraded. Non-endometrioid cancers under consideration in this study included serous carcinoma, clear cell carcinoma, and mixed epithelial adenocarcinomas, and carcinosarcoma. Other rare histologic types including sarcomas with a high variety in prognosis were excluded from this investigation. Tumor stage was defined following the American Joint Committee on Cancer (AJCC) staging system (18–23). Women who had a previous or current diagnosis of another cancer or did not have a surgical procedure for the treatment of their endometrial cancer were excluded from the analysis.

Statistical Analysis

As the first step of data analysis, we compared differences in the distribution of demographic and tumor characteristics by race using *Chi*-square test. The primary clinical endpoint for this study was all-cause survival as cause of death attributions were not consistently available. Survival times were calculated from date of diagnosis to date of death or to date of last contact or December 31, 2014, whichever occurred first for censored cases. Survival curves were generated using Kaplan-Meier method and compared using log-rank test. Finally, Cox regression, for which the proportional hazards assumption was confirmed, was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the relationship between race and survival while adjusting for potential confounding factors including age at diagnosis, diagnosis period, tumor stage, histology, and receipt of adjuvant treatment (none, radiation, chemotherapy, or combination). All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

Results

The analysis included a total of 1,583 women, 1,439 NHW and 144 NHB women. Table 1 shows the diagnosis period, tumor features, treatment, or survival status by race in this cohort. NHB women were more likely than NHW women to be diagnosed during the later period (2005 to 2013; 56.3% vs. 35.3%), have high grade endometrioid EC (18.1% vs. 10%) and have non-endometrioid histology (20.8% vs. 5.1%), respectively. Treatment with adjuvant chemotherapy was more common in NHB women vs. NHW women (18.1% vs. 8.8%).

Figure 1 shows that NHB women had worse survival than NHW women (log-rank $P<0.0001$). Table 2 indicates that NHB women had an adjusted 64% increased risk of death over NHW women (95% CI=1.19 to 2.27) after controlling for age, diagnosis period, stage, histology/grade, and adjuvant treatment. Further Cox analyses stratified by age, diagnosis period, tumor stage or histology, and adjuvant treatment demonstrated that the overall difference in risk of death between NHB and NHW women persisted within the subset with stage I/II disease (HR=1.81, 95% CI=1.17 to 2.79), low grade endometrioid carcinoma (HR=2.47, 95% CI=1.55 to 3.95), non-endometrioid cancers (HR=2.05, 95% CI=1.08 to 3.90) and those who did not receive adjuvant treatment (HR=2.15, 95% CI=1.31 to 3.53).

Discussion

This study showed that even in an equal access healthcare system, non-Hispanic Black women had significantly shorter survival than did non-Hispanic White women. This racial difference was observed in women with low risk features (stage I/II disease or low-grade) of endometrioid carcinoma, non-endometroid carcinoma, or no adjuvant treatment.

Several other studies similarly found worse survival for NHB women than their NHW counterparts. Using the SEER data, two previous studies in the general population observed worse survival among NHB women compared to NHW women even after matching on prognostic variables and stratifying by tumor characteristics such as stage and histology (24–25). Using the SEER data, Tarney et al. conducted analysis stratified by age, tumor

stage and grade, and demonstrated worse survival for Black woman compared with White women with either endometrioid carcinoma or non-endometrioid carcinoma (7). The similar findings were obtained in a study based on the National Cancer Database after controlling for factors associated with survival and stratifying by stage (26). However, previous studies conducted within the Henry Ford Healthcare System, in which members have similar access to care, found no racial differences in either all-cause or endometrial cancer-specific survival. These studies adjusted for comorbidities and biological variables unavailable in our registry data (12–13). Compared with Kost's study based on the DoD Cancer Registry data (14), which found worse cancer-free survival in Black women than White women in univariate analysis but not in analysis with adjustment for tumor stage, our study adjusted for not only tumor stage but also radiation and chemotherapy. In a multi-site study (27), in which all the study participants received surgery, racial differences in recurrence of endometrial carcinoma were observed for low-grade or early-stage tumors but not for high-grade or non-endometrial tumors. These results were similar to our findings, although the study outcome was recurrence rather than death.

Several factors might explain a poorer survival among Black women than White women when access to care is equal. First, histologic subtype may vary among racial/ethnic groups. Previous studies have reported that Black women were more likely to present with non-endometroid histologic subtypes including serous and clear cell carcinoma, which are more aggressive and have higher risks of recurrence, progression, and mortality (3, 8). This was also observed in our study, although the numbers of women with these types were too small (data not shown). Nevertheless, we adjusted for histologic type in our analysis. Second, other tumor characteristics that were not considered may have differed by race. Previous studies have suggested that the observed racial disparities could be attributed to differences in molecular features of tumors (e.g., PTEN, HER2/neu, p53 mutations, copy number variant high subtype, mitotic molecular subtype or transcript cluster 4 subtype) (7, 28–32). This information is not included in our data and could not be evaluated. Third, our study used all-cause mortality as the study outcome which included death from causes other than endometrial cancer, such as comorbid conditions. Previous research has found that comorbid conditions affect overall survival among women with endometrial cancer (12). Because Black women are more likely to have comorbidities than White women (33–36), they may be more likely to die of these medical conditions and thus have shorter overall survival. A study conducted using SEER data found that women diagnosed with endometrial cancer are more likely to die from cardiovascular disease than endometrial cancer (37). In the study by Tarney *et al.* there was worse non-cancer-related mortality among Black women with endometrial carcinoma younger than 65 years than their White counterparts, further confirming the possible effects of comorbidities (7). In our study, the observed racial differences among women with early stage or low-grade endometrial cancer and women without adjuvant chemotherapy, who have less aggressive cancer and thus may be less likely to die of endometrial cancer itself, might also imply the effects of comorbid diseases. However, the overlapping confidence intervals of HRs due to the small sample sizes in the stratified analyses prevent us from ascertaining this conjecture. Nevertheless, a separate study showed that a higher prevalence of comorbidities among Black women may not fully account for the higher mortality compared to White women (38). Fourth,

treatment effectiveness may vary between racial groups. Research has shown that while 43% of White women with endometrial cancer responded to doxorubicin and cisplatin, only 35% of Black women responded (39). Finally, Black and White women might differ in treatment intensity and completeness and therefore survival. Although our multivariable models adjusted for whether a woman received treatment, we cannot exclude the possible effects of racial differences in treatment timing, intensity, and duration.

Endometroid carcinoma constitutes a majority of endometrial cancer as also shown in our study. As described above, in the study by Felix et al., the racial differences in recurrence were observed only in women with low-risk features of endometroid carcinoma (stage I/II disease or low-grade endometrioid carcinoma) among patients who all received surgery (27). Several factors may contribute to the racial difference in these low risk patients. In addition to the potential effects of comorbidities described above, molecular features that may reflect more aggressiveness of tumors may be a factor. One of our previous studies by Dubil et al. (32) showed that Black women were more likely than White women to exhibit the somatic copy number alteration (SCNA)-based cluster 4 subtype (‘serous-like tumor’) among patients with low-grade (16.7% vs. 1.4%) or early-stage (29.6% vs. 10%) tumors. This finding might also account for why the racial difference was observed only among patients with no adjuvant treatment. Patients who received surgery but not adjuvant treatment usually have low-stage or low-grade tumors and thus the racial difference among these patients may reflect that in early-stage or low-grade tumors. Nevertheless, in the study by Dubil et al., the racial differences in these molecular features were also observed in high-grade or late-stage tumors (32). While it is not clear why the racial differences in survival were not shown in high-risk tumors assuming more aggressive tumors features in Black patients, it might result from complex effects of multiple factors such as tumor-risk related molecular features, utilization of medical care, and family support. One of the factors might be no or minimal financial barriers to and thus wide utilization of adjuvant treatment, which is more widely used for high-grade and late-stage tumors, in the Military Health System that provides universal care. As a result, racial differences in survival might be mitigated among patients with high-grade or late-stage disease or who received adjuvant treatment.

Factors related to the racial difference in non-endometroid carcinoma are unclear. Non-endometroid carcinoma consists of different histologic types varying in tumor aggressiveness. Small numbers of patients for both races prevented us from analysis by histologic subtype, tumor stage, or treatment, which may be associated with the identified racial differences.

The strength of this study is to assess racial differences in survival in an equal-access health care system. This largely minimized the impact from unequal access on survival disparity and the research findings imply potential effects of factors other than access to care. However, some limitations should be kept in mind. First, the outcome was all-cause mortality. It reflects not only endometrial cancer-specific death but also deaths of other causes, as stated above. Second, this study was based on cancer registry data, which do not contain information on lifestyle and anthropometric factors related to survival, such as obesity (40), we do not exclude the possibility of residual confounding. Third, there were

relatively small numbers of women for stratified analysis, which led to low study power for identifying the racial difference in subgroups.

In conclusion, this study suggests NHB women with endometrial cancer had poorer survival than NHW women in an equal access healthcare system, further supporting that factors other than access to care may be related to the racial disparity in survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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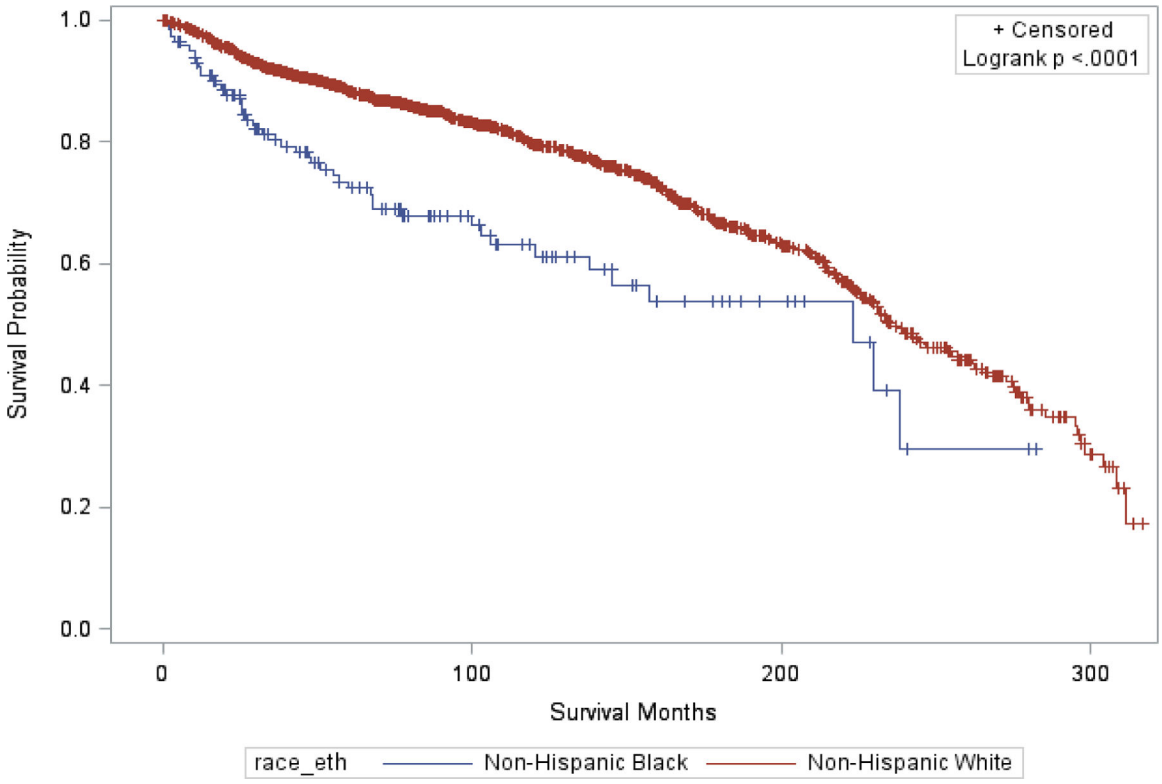

Figure 1.
Survival distribution for non-Hispanic Black vs. non-Hispanic White women in ACTUR with surgically managed endometrial cancer

Table 1.

Clinical characteristics in surgically managed non-Hispanic Black and non-Hispanic White women with endometrial cancer in ACTUR diagnosed between 1988–2013

	Non-Hispanic White (N=1,439)		Non-Hispanic Black (N=144)		*p*-value
	Cases	%	Cases	%	
Age group					0.3573
<45	132	9.2	20	13.9	
45–54	303	21.1	24	16.7	
55–64	608	42.3	60	41.7	
65–74	267	18.6	28	19.4	
75+	129	9.0	12	8.3	
Diagnosis period					<0.0001
1988–1994	303	21.1	13	9.0	
1995–2004	628	43.6	50	34.7	
2005–2013	508	35.3	81	56.3	
Stage					0.0524
Stage I	1,101	76.5	95	66.0	
Stage II	81	5.6	9	6.3	
Stage III	132	9.2	21	14.6	
Stage IV	44	3.1	8	5.6	
Unknown	81	5.6	11	7.6	
Histology					<0.0001
Endometrioid					
Low grade	1,104	76.7	78	54.2	
High grade	144	10.0	26	18.1	
Ungraded	118	8.2	10	6.9	
Non-endometrioid	73	5.1	30	20.8	
Radiation					0.1345
No	1,051	73.0	99	68.8	
Yes	349	24.3	37	25.7	
Unknown	39	2.7	8	5.6	
Chemotherapy					0.0015
No	1,297	90.1	116	80.6	
Yes	127	8.8	26	18.1	
Unknown	15	1.0	2	1.4	

Table 2.

Stratified analysis of survival in surgically managed non-Hispanic Black vs. non-Hispanic White women with endometrial cancer

	Multivariable NHB vs. NHW[a]		
	HR	**95% CI**	***p***
Overall	1.64	1.19 to 2.27	0.0024
By age group			
<65	1.30	0.81 to 2.07	0.2795
65+	1.36	0.86 to 2.15	0.1925
By diagnosis period			
1988–1994	1.04	0.41 to 2.62	0.9331
1995–2004	1.68	1.07 to 2.65	0.0241
2005–2013	1.41	0.75 to 2.68	0.2899
By stage			
Stage I/II	1.81	1.17 to 2.79	0.0076
Stage III/IV	1.05	0.59 to 1.86	0.8614
Unknown	0.88	0.22 to 3.52	0.8551
By histology			
Endometrioid low grade	2.47	1.55 to 3.95	0.0002
Endometrioid high grade	0.45	0.21 to 0.97	0.0424
Endometrioid ungraded	1.03	0.12 to 8.60	0.9788
Non-endometrioid	2.05	1.08 to 3.90	0.0277
By adjuvant treatment			
None	2.15	1.31 to 3.53	0.0026
Radiation alone	1.40	0.76 to 2.59	0.2780
Chemotherapy alone	0.83	0.36 to 1.93	0.6622
Chemotherapy and radiation	0.68	0.13 to 3.62	0.6498
Unknown	1.14	0.12 to 10.1	0.9098

[a]Hazard Ratios (HRs) for risk of death for NHB vs. NHW women adjusted for age at diagnosis (continuous), diagnosis period, tumor stage, histology, and receipt of adjuvant treatment; HRs for subgroup analysis were not adjusted for the corresponding stratified variable.