

Racial and Ethnic Disparities in Cancers of the Uterine Corpus

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Survival after diagnosis of cancer of the uterine corpus is significantly worse in black women as compared with white women. The etiology of the racial and ethnic disparities that exist in endometrial cancer incidence and outcome is multifactorial and complex. Potential explanations include cancer biology, differences in access to care, sociodemographic characteristics, response to treatment and comorbid factors. In this article, a review was performed to assess the magnitude and reasons for the observed disparity in endometrial cancer mortality. Strategies and recommendations to reduce or eliminate differences in endometrial cancer outcome are explored. These include advocacy for more research to clarify the underlying causes of cancer disparities at all levels, including the molecular basis of disparate outcomes, improving access to quality healthcare services, establishing culturally competent models of healthcare delivery, and developing novel cost-effective screening and early prevention methods.

Keywords: health disparities ■ cancer ■ race/ethnicity ■ minorities ■ women's health

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INTRODUCTION

Uterine corpus cancer is the most common invasive neoplasm of the female genital tract and accounts for approximately 6% of cancers in women in the United States.¹ In 2006, an estimated 41,200 new cases and 7,350 deaths from cancer of the uterine corpus will have occurred. Of these, 3,080 new diagnoses and 1,150 deaths were projected among black women in 2005. Non-Hispanic white women have the highest age-adjusted incidence of invasive cancer of the corpus (25.4/100,000 women), while women of black, Hispanic, and Asian/Pacific Islander heritage have significantly lower incidences of malignant tumors of the uterine corpus (19.5/100,000, 17/100,000 and 15.8/100,000, respectively).² Black women, however, experi-

ence a substantially greater mortality rate—almost twice that of white women (7.1/100,000 vs. 3.9/100,000). This poorer outcome is reflected by a 60.9% five-year survival rate for black women with endometrial cancer, compared with 84.4% for white women between 1996 and 2002.² The determinants of the excess endometrial cancer mortality experienced by black women have been explored with respect to socioeconomic and cultural issues, access to care, tumor-associated biologic factors, comorbid illnesses and genetics.

Endometrial cancer primarily affects postmenopausal women. Risk factors include obesity, nulliparity, late menopause, diabetes, hypertension and exogenous unopposed estrogen. The vast majority of malignant corpus tumors are endometrial adenocarcinomas. Of these, endometrioid adenocarcinoma, which often arises in the setting of hyperplasia secondary to excess estrogen, is the predominant histopathological subtype. Part of the higher mortality among blacks is thought to be due to differences between blacks and whites in the incidence rates of specific histopathological types of endometrial cancer and, consequently, in the behavior of the malignant tumors.³⁻¹² Numerous studies have demonstrated that aggressive corpus tumors, such as serous and clear-cell carcinomas, carcinosarcoma and sarcoma, account for a disproportionately high percentage of corpus cancers in black women.³⁻¹² These aggressive histologic subtypes of endometrial cancer tend to arise from atrophic endometrium and are less strongly associated with high body mass index, exogenous estrogen use and elevated serum levels of estrogen. The more frequent presentation with aggressive, poor prognosis tumor among black women, therefore, likely reflects differences in etiologic exposure and genetics compared with white women.

Studies have revealed that not only do black women present more frequently with unfavorable histologic types of uterine cancer, they are also more likely to have advanced-stage, poorly differentiated tumors,^{3-9,13} with additional adverse pathologic features.¹⁴⁻¹⁶ The Black/White Cancer Survival Study concluded that the black/white disparity in stage distribution, which is related to the increased frequency of aggressive histologic types of carcinoma,^{3,7} accounted for 43% of the difference in endometrial cancer survival.⁵ Also notable, however, is that within each histo-

logic type, including the more common and better prognosis endometrioid adenocarcinoma, black women tended to have more advanced-stage disease and fared worse, compared with whites.^{8,11} The estimated mortality rate for blacks with endometrioid tumors was 2.35/100,000, compared with 1.98/100,000 for whites.^{8,11} Greater differences were observed for aggressive serous and clear-cell tumors as well as carcinosarcomas. Sherman et al. estimated that 53% of the total mortality among blacks, compared to 36% among whites, was associated with unfavorable histology.¹¹

Recently, molecular alterations involved in the pathogenesis of endometrial cancer have been elucidated. Of these, several events may contribute to the racial disparity in survival. Overexpression of the mutant p53 protein as a result of mutations in the TP53 gene correlates with aggressive clinical behavior in endometrial cancers. The TP53 tumor suppressor gene is a key regulator of cell cycle progression and apoptosis. In endometrial cancer, loss of p53 function and overexpression of the mutant p53 have been associated with nonendometrioid histology, advanced stage and poor outcome,^{17,18} as well as recurrent disease.¹⁴ p53 overexpression was more common in black women with both early- and advanced-stage cancers as compared to white women, thus suggestive of a contributory role to the observed black/white disparity in overall survival.^{14,15}

Conversely, mutations of the PTEN tumor suppressor gene and microsatellite instability are associated with favorable clinicopathologic features and outcome.¹⁹ PTEN mutations are up to four-fold more frequent in whites relative to blacks.²⁰ It has been postulated that perhaps p53 is a more frequent target for mutations than PTEN in black women, thus accounting for the higher nonendometrioid cancers in the former and resulting poorer outcomes. Microsatellite instability, on the other hand, does not appear to contribute to the racial disparity in survival in this patient population.¹⁹ It is a molecular phenotype present in approximately 20–25% of nonfamilial endometrial cancers and reflects an underlying defect in DNA mismatch repair processes.²¹ No differences in frequency of microsatellite instability were identified among black and white patients.

More recently, aberrant HER2/neu oncogene expression has been identified in black patients with uterine papillary serous cancers leading to the hypothesis that the higher frequency of HER2/neu overexpression in blacks may contribute to the disparity in survival.¹⁶ Additionally, provocative data from high throughput studies using DNA microarray analyses suggest that distinct patterns of gene expression may characterize black and white women with advanced-stage endometrial cancer.²² In fact, 325 gene transcripts showed different levels of expression in black and white women with endometrial cancer. Taken together, these data suggest that differences in the molecular events involved in endometrial cancer development may contribute to the observed survival disparity.

Nevertheless, the causes of the discordance in overall

survival between black and white women with endometrial cancer are likely multifactorial. A prior report from the National Cancer Database found that black women were less often treated surgically at all stages of disease, and received adjuvant radiotherapy less frequently and chemotherapy more often than white patients.⁴ This study, however, did not explicitly examine the association between treatment and survival. Nonetheless, a more recent analysis by Randall and Armstrong using SEER data also showed a lower rate of surgery among black women at all stages of disease.²³ Among patients with localized stage-1 disease, 2.2% of white women did not undergo surgery whereas 7.7% of black women did not receive surgical therapy. Interestingly, the reduction in mortality associated with use of surgery, however, was significantly less among black women than white women (HR: 0.44, 95% CI: 0.32–0.59 vs. HR: 0.26, 95% CI: 0.23–0.29).²³ It is important to treat these findings cautiously and recognize that the association between surgery and survival may not be causal, since both staging and therapeutic procedures are performed during endometrial cancer surgery.

Conversely, several single institution studies^{6,7,12,24,25} and one population-based analysis¹³ did not find differences in treatment that might explain the observed survival disparities. Studies conducted to evaluate delay in seeking treatment did not identify differences in the interval from onset of symptoms to diagnosis and/or hysterectomy among blacks and whites;^{6,7} nor were there differences in the recommendation and receipt of guideline therapy between black and white women (84% and 88%, respectively).¹³ Maxwell et al. confirmed that in a cohort of patients who received similar care in the setting of a clinical trial, black women with advanced (stage 3/4) or recurrent endometrial cancer had a lower survival compared to white women.²⁶ Median survival was 10.6 months for black women and 12.3 months for white women (HR: 1.33, 95% CI: 1.11–1.61). Multivariate regression analysis revealed that more-advanced stage, histology and grade were independent poor prognostic factors.²⁶

Others have documented that lower socioeconomic status and greater medical comorbidity contribute to worse outcomes among black women.^{3-5,12,24,27} Hicks et al. previously found that limited income was associated with a lack of treatment for black women with stage-4 disease.⁴ Increased frequency of clinical comorbid factors among black women was documented for patients with endometrial cancer in the Black/White Cancer Survival Study.⁵ In this study, black women were more than twice as likely as white women to be overweight, diabetic and hypertensive—all of which are known risk factors for developing endometrial cancer. Therefore, greater medical comorbidity, together with reduced access to care through social or economic factors, and potential differences in extent of disease within each stage are possible reasons why black women are less likely to undergo surgical therapy. These variables have been implicated in similar racial disparities

seen in the use of various surgical procedures, including renal transplantation and coronary artery catheterization.

Nevertheless, even after accounting for these factors, significant differences in mortality rates persist. In fact, Sherman and Devesa showed that for every stage, grade and age group, survival for black women was worse than for white women.¹¹ The most striking racial disparities were with respect to local-regional-staged disease, high-grade tumors and women >55 years old at diagnosis, where the five-year survival rates were 38.3% vs. 72.7%, 38.7% vs. 62.5%, and 66.5% vs. 89.8%, respectively, for blacks and whites.¹¹

This review has focused on the disparity between blacks and whites because the majority of research examining race as a prognostic factor has been directed toward studying these two ethnic groups. One study of women treated in the U.S. Department of Defense medical system has suggested that Asians/Pacific Islanders also have a worse survival rate, compared with white women at all stages of disease.²⁸ Five-year survival for this cohort was 91% for whites, 72% for blacks and 77% for Asians/Pacific Islanders. Similar to the black women in the study, Asians/Pacific Islanders had higher frequencies of tumors with unfavorable histologies and high-grade lesions. Interestingly, however, Asians/Pacific Islanders did not appear to have significantly more advanced-stage disease, compared to whites. Plaxe and Saltzstein in their analysis of the California Cancer Registry data set revealed that the frequency of poor prognosis and high-grade tumors was quite similar among all the ethnic groups (white, black, Hispanic, Asian/other); it was the risk of developing the more common, low-risk cancer that was variable.¹⁰

In summary, multiple factors appear to contribute to the black/white disparity in endometrial cancer mortality. The observed racial imbalances are attributable to the combination of: 1) the higher incidence of aggressive subtypes of uterine corpus cancers in black women; 2) the higher mortality among black women compared to white women at each stage and grade of tumor, including those with favorable prognosis; 3) failure to access quality healthcare service; 4) and failure to receive standard of care. A growing body of literature on the molecular events implicated in the pathogenesis of endometrial cancer suggests that differences in tumor biology are important determinants of outcome, with certain events possibly being more prevalent in specific ethnic groups. It is likely that complex interrelationships among race, culture, socioeconomic status, comorbid factors and molecular events contribute to the different survival rates seen in women of different ethnicities with uterine corpus cancers. The magnitude of effect of molecular versus economic equality and cultural factors remains to be determined. It is hopeful that continued research on the molecular heterogeneity of endometrial cancers and further characterization of the molecular correlates of the observed racial disparity will hopefully lead to better individualization of treatment and improved out-

comes for all.

Innovative strategies must be explored at multiple levels—molecular, individual and societal—to impact existing racial and ethnic disparities in cancers of the uterine corpus. There is a need to identify more effective therapy for women with high-risk or advanced endometrial cancer and to develop integrative intervention strategies to educate women, healthcare providers and the community about the disease. Rigorous scientific information about endometrial cancer needs to be disseminated to the community to increase public health awareness. While no screening examinations for cancer of the uterus are recommended for asymptomatic women, the most common symptom in up to 90% of women is postmenopausal bleeding. Prompt evaluation of this early presenting symptom allows for 70–75% of women to be diagnosed with surgical stage-1 disease. It is, therefore, critically important to educate the public to present for care early.

Concrete solutions to address issues affecting healthcare delivery to the underserved are needed. These can only be implemented with clarification at both the systemic and individual level of the factors contributing to the currently observed disparities. Specific barriers encountered by cultural minorities must be identified for appropriate changes to be made. More research in the areas of community health, population-based, health policy and behavioral sciences are needed to better understand cancer screening knowledge, attitudes, perception and behavior among the underserved. Improved understanding of the patient's cultural values and beliefs through culturally competent care models and by culturally aware healthcare providers are critical to forming a respectful relationship to positively influence the patient's outcome. Strategies specific to different geographical regions, urban versus rural communities, diverse immigrant or ethnic minority communities can help break down barriers to care.

In conclusion, despite the progress in medical technology, abundance of healthcare resources and better cancer survival in the United States, various subgroups of the population have not benefited equally. Available data point to a discordance in outcomes for black as compared to white women with endometrial cancer, among other cancers. It is hopeful that the initiatives forthcoming from the National Cancer Institute Center to reduce cancer health disparities will foster a sense of urgency and cooperation at all levels of society to reduce the unequal burden of cancer in the United States.

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