



Marguerite Bride. *St. Joe's on North Street*. Watercolor, 14" × 30".

*Continued study is needed to address the factors that contribute to the higher incidence and inferior outcomes from endometrial cancer in black women compared with white women in the United States.*

## Race Disparities Between Black and White Women in the Incidence, Treatment, and Prognosis of Endometrial Cancer

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**Background:** Uterine cancer is the most common gynecologic malignancy in the United States, with an estimated 40,100 new cases and 7,470 deaths occurring in 2008. Although the incidence of endometrial cancer is lower among black women compared with white women, the proportion of cancer-related deaths among blacks is higher and has continued to rise over the past two decades.

**Methods:** The authors conducted a survey of recent literature published in the English language and have used these articles as the basis for this review.

**Results:** The etiology for the racial disparity among black women with endometrial cancer is multifactorial and may be the result of barriers that impede access to care, an increased incidence of comorbidities among black women, inequalities in surgical care, adjuvant chemotherapy and radiation treatment, and underlying biological differences associated with more aggressive tumors that often develop in black women.

**Conclusions:** Black women with endometrial cancer have a poorer prognosis compared with white women. Factors that contribute to this racial disparity include later diagnosis, treatment disparities, comorbid conditions, and genetic differences in tumors. An improved understanding of the causative factors associated with racial disparities in endometrial cancer outcome is needed to facilitate efforts aimed at correcting this important health care problem and providing individualized care to those at highest risk for poor outcome.

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### Introduction

According to the American Cancer Society, an estimated 40,100 new cases of uterine cancer were diagnosed in 2008, the majority of which occurred in white women. The incidence of endometrial cancer was 33% lower in black women,<sup>1</sup> which may be due in part to an underestimation of endometrial cancer in this population. Because population-based estimates of incidence are inclusive of patients who have had a hysterectomy, the higher prevalence of hysterectomy for benign gynecologic conditions observed among black women

may lead to an underestimation of their endometrial cancer burden.<sup>2,3</sup>

Approximately 7,470 women with endometrial cancer died of their disease in 2008. The mortality rate is approximately 80% higher in black women with endometrial cancer than in white women, resulting in almost 1,000 deaths among blacks annually.<sup>1</sup> Approximately 14% of endometrial cancer-related deaths occur in black women, while only 7% of newly diagnosed patients are black.<sup>4</sup> Although the number of new cases presenting each year has been relatively stable, the number of deaths per year among women with this disease, particularly among blacks, is increasing.<sup>5</sup>

Several factors may contribute to the disproportion between black and white women in the incidence, treatment, and prognosis of endometrial cancer (Table). An evaluation of several of these factors is discussed below.

### Access to Care

A delay between the onset of symptoms and the diagnosis with subsequent treatment may potentially lead to more advanced disease at the time of diagnosis, ultimately resulting in worse outcome. This interval may be adversely affected by cultural and social dynamics (eg, mistrust of the health care system, difficulties in cross racial patient-physician communication) that prevent a patient from seeking medical attention.<sup>6</sup> In a study of 219 patients who underwent surgical staging for endometrial cancer, investigators evaluated racial differences regarding the interval between the onset of symptoms and the performance of a hysterectomy. Although the overall median interval was similar between blacks and whites (11.1 weeks and 13.7 weeks, respectively), women in this study who used hormone replacement therapy were more likely to have a prolonged interval between onset of symptoms and definitive surgery. Since black women were less likely to use hormones, the black women in this study would have been biased to seek medical attention sooner. Multivariate regression of endometrial cancer survival in these patients found a racial disparity in multiple clinico-pathologic factors, with black women having a significantly higher incidence of unfavorable features, even after controlling for hormone use.<sup>7</sup>

Limited financial resources and a lack of insurance are obstacles for black women seeking care within some health care systems. Madison et al<sup>8</sup> performed a multivariate analysis that concluded women with a low socioeconomic status tend to have a higher likelihood of advanced-stage disease at the time of diagnosis. Black women were 41% more likely to present with advanced-stage disease even after accounting for tumor grade, histology, and age. Race and socioeconomic status were found to be collinear in regression analysis, prohibiting an accurate determination of the independent contributions of each variable to advanced-stage disease. Fur-

**Table. — Factors That May Contribute to Racial Disparities**

Access to care	Late diagnosis	Treatment disparities
Comorbidities	Tumor genetics	Poor prognosis

ther analysis has revealed that among patients with aggressive tumor histology (ie, clear cell, serous, and undifferentiated), age, race, and median family income were not associated with advanced stage at diagnosis. However, among patients with favorable tumor histology (endometrioid and mucinous), either socioeconomic status or race was associated with advanced-stage disease in a multivariate model. Improved access to care may therefore benefit black patients and financially disadvantaged women with endometrial cancer, particularly those who develop tumors with more favorable histology. Patients with aggressive tumors may also have a more advanced stage at the time of diagnosis irrespective of race or socioeconomic status.<sup>8</sup>

### Comorbid Conditions

Comorbid conditions may play a role in the increased mortality rate for black patients with endometrial cancer. Obesity and its related diseases (eg, cardiovascular related disease, diabetes) are increased among blacks compared with whites.<sup>9</sup> Almost 77% of black women are overweight (body mass index [BMI]  $\geq$  25), and 50% are obese (BMI  $\geq$  30).<sup>10</sup> In a case control study of over 62,000 women from the Netherlands Cohort Study on Diet and Cancer, women with a BMI  $\geq$  30 had an increased risk of endometrial cancer (rate ratio = 2.57, 95% confidence interval = 1.32–4.99).<sup>11</sup> Physical inactivity, often associated with obesity, has been shown to be an independent risk factor for developing endometrial cancer.<sup>12</sup> Women who spend 90 minutes per day doing non-occupational physical activities have been shown to have a 50% lower risk of endometrial cancer compared with women who spend less than 30 minutes per day. These comorbid conditions may affect the risk of endometrial cancer among some minority women.<sup>11</sup> Black women are more than twice as likely as white women to develop type 2 diabetes. This increased risk remains despite controlling for BMI and waist-to-hip ratio, suggesting that factors other than obesity alone might be contributing to the increased risk of diabetes in this minority population.<sup>13</sup> Diabetes is associated with insulin resistance, lower sex hormone-binding globulin, and a hyperestrogenic milieu, all of which can increase the risk of developing endometrial cancer.<sup>14</sup> Although endometrial cancers that develop among diabetic patients do not appear to be pathologically or clinically different from endometrial cancers that develop in non-diabetic patients,<sup>15,16</sup> mortality is increased among endometrial cancer patients with diabetes compared to those without.<sup>17</sup>

## Treatment Factors

Inequity in treatment may be an important etiologic factor associated with poor outcome observed in black women with endometrial cancer.<sup>17</sup> In an analysis of data from approximately 55,000 patients with endometrial cancer contained in the National Cancer Data Base, investigators found that 9% of black patients did not receive any cancer-directed treatment compared with only 4% of white women. Among those who received treatment, black women tended to present with more advanced disease than white women, often requiring lymph node dissection.<sup>18,19</sup> When the data were stratified according to stage, however, the rates of hysterectomy were similar between blacks and whites. Conversely, other investigators using data from the Surveillance, Epidemiology, and End Results (SEER) programs found that rates of hysterectomy are lower among blacks compared with whites when controlling for stage of disease at diagnosis.<sup>8,18,20</sup> By using retrospective, population-based data, it is difficult to ascertain why black patients might not undergo surgery as often. In one SEER analysis, investigators found that the most common reason for not having a hysterectomy was “contraindicated/not recommended.” However, further analysis was not performed because of limitations in the uniformity of recording these data across the institutions.<sup>8</sup> Although blacks present with more advanced disease and also have a higher likelihood of comorbidities that might influence whether to perform surgery, it is also possible that discriminatory practices by some health care providers or systems play a role.<sup>8</sup> In contrast, a pattern of care analysis of the SEER data base did not identify any differences in primary or adjuvant therapy between blacks and whites with endometrial cancer when evaluating 711 women with newly diagnosed endometrial cancer.<sup>21</sup> Primary surgery also was similar between the groups that were evaluated.<sup>21</sup> Adjuvant postoperative radiotherapy has also been shown to be similar among blacks and whites, particularly among patients with local disease.<sup>8,20</sup> Similarly, administration of chemotherapy, which is usually reserved for patients with distant metastasis, has not been observed more often in black patients compared with whites.<sup>8,18</sup>

Response to surgery and chemotherapy may also differ between blacks and other patients. In another analysis of SEER data, Randall et al<sup>20</sup> noted that the association between surgery and survival was weaker among black women than in white women (hazard ratio = 0.44 vs 0.26). However, comorbidities that may have been increased in black women were not controlled for in this analysis. Additionally, treatment differences by a subspecialty gynecologic oncologist, as opposed to another subspecialist, can potentially impact outcome among black patients with endometrial cancer since patients managed by another specialist may be less likely to be surgically staged and more like-

ly to receive radiation therapy.<sup>22,23</sup> A recent meta-analysis performed by the Gynecologic Oncology Group (GOG) reported a lower response rate for patients with advanced-stage and recurrent endometrial cancer who received chemotherapy on one of four randomized controlled trials. In this analysis, black women had an overall response rate of 34.9% compared with 43.2% for whites.<sup>24</sup> Although there was no difference in the proportion of black and white patients completing all cycles for the regimen received, there was no information regarding dose reductions or delays that may have biased this observation. Further investigation of differences in response to either surgery or chemotherapy treatment is necessary.

## Molecular and Genetic Alterations

Black patients with newly diagnosed endometrial cancer often present with advanced-stage, poorly differentiated, non-endometrioid type tumors when compared with white women.<sup>24</sup> Population studies have shown that black women have a higher incidence of tumors with non-endometrioid histology rather than a decreased proportion of indolent tumor types.<sup>25</sup> Sherman and Devesa<sup>25</sup> reported that 53% of the total mortality among black patients was associated with non-endometrioid tumors compared with only 36% among white patients.

Our group has recently performed an analysis of data from the GOG regarding advanced-stage and recurrent endometrial cancer in an effort to determine whether black women have a worse survival than white women when receiving similar treatment for endometrial cancer while participating in a randomized cooperative group clinical trial.<sup>26</sup> Multivariate regression revealed a 26% greater chance of dying among black patients compared with white patients, even when controlling for multiple comorbidities, stage, histology, tumor grade, performance status, and BMI.<sup>26</sup> These findings do not negate the importance of these variables in contributing to the racial disparity in outcome among patients with endometrial cancer. Instead, they suggest that other factors may play a role in the disparity in outcome observed in patients with endometrial cancer.

Evaluation of potential genetic and epigenetic etiologies for differences in observed tumor behavior has been performed utilizing molecular analysis of endometrial cancers from blacks and whites. Mutations in the *TP53* tumor suppressor gene, which is associated with poor outcome, have been reported to be present twice as often in endometrial cancers from black patients compared with white patients (55% vs 25%).<sup>27</sup> Additionally, racial disparity in overexpression of the Her-2 oncogene, which is also associated with shortened survival, has been observed more often in blacks compared with whites (70% vs 24%).<sup>28</sup> Alterations of the *PTEN* tumor suppressor gene, paradoxically associated with favorable outcome, are more common in white

women with endometrial cancer than in black women (22% vs 5%).<sup>29</sup> In addition to mutational events, methylation of a gene's promoter region may be one epigenetic mechanism affecting gene expression that can contribute to the development and progression of endometrial cancer. Investigations of potential epigenetic influences on racial disparity have evaluated methylation of ribosomal DNA and found that endometrial cancers from black patients demonstrate significantly more ribosomal DNA methylation than tumors from white patients.<sup>30</sup> Although each of these molecular analyses suggests a potential biological etiology for racial differences in outcome, studies have been limited in terms of being able to show associations between molecular alterations and outcome while controlling for other prognostic factors. These investigations imply that the cancers in black women more often develop with a molecular background disposed to more aggressive disease, whereas those in white women more often develop from a differing set of defects that tend to result in cancers that are less aggressive.

## Conclusions

Black women with endometrial cancer have a poorer prognosis than white women have, and the etiology for this racial disparity is multifactorial. Factors include later diagnosis, treatment disparities, comorbid conditions, and genetic differences in tumors. The rise in cancer-related mortality from endometrial cancer in black women continues to be a problem that has not yet been controlled.

According to the 1997 US Census, the black population in the United States is expected to nearly double to 61 million by 2050.<sup>31</sup> Improved public awareness regarding health disparities research is needed to address health care issues in this increasing population of patients. Additional research should seek to clarify the underlying causes of cancer disparities and, more importantly, develop strategies to remove the barriers that adversely affect optimal detection and treatment of underserved minority populations.

## Disclosures

*The opinions or assertions expressed in this article represent the private views of the authors and should not be construed as reflecting the official views of the Department of the Army, the Department of the Navy, or the Department of Defense.*

*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

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