The Impact of Race and Comorbidity on Survival in Endometrial Cancer

Sara H. Olson1, Coral L. Atoria1, Michele L. Cote2, Linda S. Cook3, Radhai Rastogi1, Robert A. Soslow1, Carol L. Brown1, and Elena B. Elkin1

Abstract

Background: Poorer survival from endometrial cancer in blacks than in whites is well documented. The aims of this study were to determine whether diabetes, hypertension, or other conditions influence survival and whether accounting for these conditions reduces this racial disparity.

Methods: Using the SEER-Medicare database, we investigated the influence of diabetes, hypertension, and other comorbid conditions on survival in black and white women age ≥66 with endometrial cancer. We used Cox proportional hazards regression to evaluate the influence of comorbidities on survival for blacks and whites separately and to study survival differences between blacks and whites after adjustment for diabetes, hypertension, and other medical conditions, as well as for demographics, tumor characteristics, and treatment.

Results: In both racial subgroups, women with diabetes or other conditions had poorer overall survival, whereas hypertensive black women experienced better survival [HR, 0.74; 95% confidence interval (CI), 0.60–0.92]. For disease-specific survival, diabetes was associated with poorer survival in white women (HR, 1.19; 95% CI, 1.06–1.35) but not in blacks (HR, 0.97; 95% CI, 0.73–1.30); hypertension and other conditions were not significantly related to survival. After adjustment, black women had poorer survival than white women, with HRs of 1.16 (95% CI, 1.05–1.28) for overall and 1.27 (95% CI, 1.08–1.49) for disease-specific survival.

Conclusions: Diabetes influences disease-specific survival in white women but not in blacks. The racial disparity in survival is not explained by the presence of other health conditions.

Impact: Further research should focus on the unknown factors that lead to poorer survival in black women compared with whites. Cancer Epidemiol Biomarkers Prev; 21(5); 753–60. ©2012 AACR.

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States with more than 47,000 new cases per year (1). There is a large disparity in outcomes between blacks and non-Hispanic whites while the annual incidence rate for black women is lower than that for whites, 21.5 versus 26.0 per 100,000, the mortality rate is almost twice as high, 7.1 versus 3.9 per 100,000 (2). Among women aged ≥65, similar disparities exist: incidence is lower in blacks than in non-Hispanic whites (83.8 vs 87.9 per 100,000) but mortality is almost twice as high in black women (38.2 vs 21.4 per 100,000) (2). The reasons for this disparity in survival have been investigated in a number of studies. Black women are diagnosed with later stage, higher grade disease, and with the more lethal histologic types; however, survival is less favorable at every stage, grade, and for every histologic type (3–7). Results from clinical trials, with uniform eligibility requirements and treatment, also show poorer outcomes for black women, suggesting unknown biologic differences in hosts or tumors (8). Consistent with differences in histologic types, endometrial tumors in black women have less favorable molecular features (9–12).

One aspect of this disparity in survival that has not been thoroughly considered is the presence of comorbid medical conditions and their influence on survival. In particular, diabetes and hypertension are more prevalent in blacks than in whites (13) and some studies suggest that presence of diabetes is associated with poorer survival in women with endometrial cancer (14–17). We used the population-based SEER-Medicare database to assess the influence of medical conditions on overall and disease-specific survival in older women with endometrial cancer and to determine whether these factors explained part of the disparity in outcome between blacks and whites.
Materials and Methods

Data sources

Our sample was obtained from SEER cancer registry data linked with Medicare claims. SEER, a program of the National Cancer Institute, is a consortium of population-based cancer registries in 17 regions of the United States, covering about 28% of the U.S. population. For all incident cancers in their coverage areas, the SEER registries collect data about the site and characteristics of disease (stage, grade, and histology), the first course of cancer-directed therapy, prior cancer diagnosis, and sociodemographic characteristics (age, race, Hispanic ethnicity, and marital status). SEER registries also conduct active follow-up for date and cause of death. For patients with cancer aged ≥65 residing in SEER areas, Medicare claims have been linked to SEER files. Medicare is the primary health insurer for 97% of Americans ages 65 years and older, covering inpatient hospital care (part A) and outpatient care and physician services (part B). Compared with the U.S. elderly population, the SEER-Medicare population has similar age and sex distributions but has a smaller proportion of non-whites and a higher proportion living in urban and affluent areas (18).

Study cohort

In the SEER-Medicare database, we identified all women age 66 and older diagnosed with endometrial cancer (ICD site 54.1 or 54.9) between 2000 and 2005. We excluded women aged 65 at diagnosis to ensure at least 1 full year of Medicare claims before diagnosis for identifying comorbid conditions. Women who were diagnosed only at the time of death, who were enrolled in a managed care plan before diagnosis or at any time after diagnosis, or lacked complete Medicare coverage (parts A and B) were excluded. We included only women identified by SEER as non–Hispanic white or black.

Comorbid conditions

The conditions of interest were diabetes, hypertension, and other comorbid illness. We used a validated algorithm (19) to determine presence of diabetes based on Medicare claims within the 2 years before endometrial cancer diagnosis (or within 1 year before diagnosis for women aged 66 at diagnosis). Hypertension was defined by the presence of 2 Medicare claims at least 30 days apart containing ICD-9 codes 401, 402, 403, or 404. Information about “other comorbid conditions” was obtained using an adaptation of the Charlson Index (20), based on both inpatient and outpatient claims. The time frame for both hypertension and other conditions was >1 month and <1 year before endometrial cancer diagnosis. Because diabetes was identified separately, we excluded it from the Charlson score. Hypertension is not included in the Charlson Index.

Patient and disease characteristics

Using information from SEER, we categorized tumor stage into 4 groups: FIGO IA/IB/IIA; FIGO IC/IIIB/IIIA; FIGO IIIB-IVB; and unknown. Tumor histology was also classified in 4 groups (Supplementary Table 1): Type I consisted of endometrioid tumors or adenocarcinomas; Type II included less common types that have poorer prognosis, primarily serous, papillary, and clear cell tumors; Type III included the rare and more lethal Mullerian and mesodermal mixed tumors; and the fourth group consisted of unknown histologic type. Using information from both SEER and Medicare, we identified treatments for endometrial cancer within the year following diagnosis (Supplementary Table 2). These included surgical procedures, radiation therapy, and chemotherapy. Marital status, geographic region, and year of endometrial cancer diagnosis were identified from SEER. Information on education and income was not available for individuals but was estimated from census tract data.

Statistical analyses

The characteristics of black and white women with endometrial cancer were compared with respect to demographic, tumor, and treatment characteristics and presence of diabetes, hypertension, and other comorbid conditions using χ² statistics. We also compared women with and without diabetes, hypertension, and other conditions with respect to tumor characteristics and treatment. Kaplan–Meier methods were used to describe overall and endometrial cancer–specific survival in blacks and whites. We also compared the cumulative incidence of endometrial cancer death in white and black women, treating deaths from other causes as a competing risk (21). HRs were estimated from Cox proportional hazards models for overall and disease-specific survival for black and white women separately, with adjustment for factors related to demographics, tumor characteristics, and treatment. Interactions between race and diabetes, hypertension, and other conditions were evaluated by adding interaction terms to models including all women. Cox models were also used to evaluate overall survival and endometrial cancer–specific survival for black women relative to whites. In these analyses, covariates related to age, tumor characteristics and treatment, demographics, and year of diagnosis were included in the model, followed by addition of diabetes, hypertension, and other conditions. “Unknown” variables were included as separate categories in multivariate analyses. The proportional hazards assumptions were met in our data.

Results

Characteristics of black and white patients with endometrial cancer

There were 11,610 white and 958 black women in the cohort. Black women were younger than white women, were more likely to be unmarried (70% vs. 54%) and to live in neighborhoods with low median income (62% vs. 20%) and low educational attainment (74% vs. 28%; Table 1). They were more likely to live in urban areas (91% vs. 84%) and in the South (35% vs. 14%). As expected, tumors in
black women were higher stage and higher grade and were less likely to be type I endometrial carcinoma. Black women were considerably less likely to have had surgery (74% compared with 89% of whites) and more likely to have been treated with radiation (41% vs. 36%) or chemotherapy (19% vs. 14%). Black women were more likely to have diabetes (41% vs. 22%) and hypertension (73% vs. 52%) as well as one or more other comorbidities (29% vs. 20%); they were less likely to have had a previous cancer diagnosis (7% vs. 12%).

Clinical characteristics of patients with and without diabetes, hypertension, and other conditions

Patients with diabetes or other conditions were somewhat less likely to be diagnosed at the earliest stage, and those with other conditions were less likely to have the lowest grade tumors (Table 2). In general, the differences observed were small and statistical significance was partly due to higher proportions of those with unknown tumor characteristics among those with diabetes or other conditions. Presence or absence of hypertension was not related to tumor characteristics. Women with diabetes, hypertension, or other conditions were less likely to have surgery. Those with diabetes were more likely to have radiation, whereas those with other conditions were less likely to have chemotherapy.
Table 2. Clinical characteristics of the cohort by presence of diabetes, hypertension, and other comorbid conditions

<table>
<thead>
<tr>
<th></th>
<th>Diabetes (N = 2,974), %</th>
<th>No Diabetes (N = 9,594), %</th>
<th>P</th>
<th>Hypertension (N = 6,754), %</th>
<th>No hypertension (N = 5,814), %</th>
<th>P</th>
<th>Charlson score ≥ 1 (N = 2,614), %</th>
<th>Charlson score = 0 (N = 9,954), %</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Clinical stage (FIGO)</td>
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<tr>
<td>IA, IB, IIA</td>
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<td></td>
<td>&lt;0.0001</td>
<td>56 57</td>
<td></td>
<td>0.09</td>
<td>52 57</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>IC, IIb, IIIA</td>
<td>30 30</td>
<td></td>
<td></td>
<td>30 30</td>
<td></td>
<td>0.09</td>
<td>29 30</td>
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<td>&lt;0.0001</td>
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<tr>
<td>IIIB-IVB</td>
<td>8 8</td>
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<td>8 8</td>
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<td>0.09</td>
<td>9 8</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Unknown</td>
<td>7 5</td>
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<td>6 5</td>
<td></td>
<td>0.09</td>
<td>9 5</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Tumor grade</td>
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<td></td>
<td>0.61</td>
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<tr>
<td>I</td>
<td>29 31</td>
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<td>II</td>
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<td>0.61</td>
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<td>III</td>
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<td>19 17</td>
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<tr>
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<td>82 82</td>
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<td>0.21</td>
<td>5 4</td>
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<td>0.07</td>
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<tr>
<td>Treatment within 1 y</td>
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<tr>
<td>Surgery</td>
<td>82 89</td>
<td></td>
<td>&lt;0.0001</td>
<td>86 89</td>
<td></td>
<td>&lt;0.0001</td>
<td>76 90</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiation</td>
<td>38 35</td>
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<td>0.003</td>
<td>36 35</td>
<td></td>
<td>0.24</td>
<td>35 36</td>
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<tr>
<td>Chemotherapy</td>
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<td></td>
<td>0.34</td>
<td>14 15</td>
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<td>0.11</td>
<td>11 15</td>
<td></td>
<td>&lt;0.0001</td>
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</table>

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Diabetes, hypertension, and other conditions and survival

With median follow-up of 3.5 years, there were 5,123 deaths including 1,691 from endometrial cancer. As shown in Table 3, diabetes was associated with death from any cause in both racial subgroups: adjusted HR, 1.27 (95% CI, 1.18–1.36) and adjusted HR, 1.30 (95% CI, 1.08–1.56) for whites and blacks, respectively. Poorer overall survival was also found in those with a Charlson score ≥2, with adjusted HR, 1.62 (95% CI, 1.46–1.80) and HR, 1.81 (95% CI, 1.42–2.32) for whites and blacks, respectively. Hypertension was related to more favorable survival in black women: HR, 0.74 (95% CI, 0.60–0.92) but was not related to survival in white women: adjusted HR, 0.94 (95% CI, 0.89–1.01).

For death from endometrial cancer, diabetes was associated with poorer outcomes among white women (HR, 1.19; 95% CI, 1.06–1.35) but not among black women (HR, 0.97; 95% CI, 0.73–1.30); the interaction between race and diabetes was not statistically significant (P = 0.16). Hypertension was not associated with cancer-specific survival in white women (HR, 1.07; 95% CI, 0.96–1.19). Black women with hypertension had somewhat better cancer-specific survival than those without hypertension, although this association was not statistically significant (HR, 0.76; 95% CI, 0.55–1.05). The interaction between hypertension and race was statistically significant (P = 0.007). Other comorbid conditions were not significantly related to cancer-specific survival in either group (Table 3).

Survival in black women compared with white women

Both overall and disease-specific survival were considerably poorer for black women than for whites (Fig. 1). The survival advantage for whites was also evident in a competing risk analysis, where the cumulative incidence of endometrial cancer death was greater for black women than white women (P < 0.001). For overall survival, the unadjusted HR for blacks compared with whites was 1.86 (95% CI, 1.71–2.04), shown in Table 4. Adjustment for disease characteristics and treatment and for demographic characteristics

![Figure 1. Overall and disease-specific survival in black and white women with endometrial cancer in SEER-Medicare cohort.](image)

### Table 3. Impact of comorbid conditions on survival in white and black women with endometrial cancer

<table>
<thead>
<tr>
<th></th>
<th>White women (N = 11,610)</th>
<th>Black women (N = 958)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR* (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.27 (1.18–1.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.94 (0.89–1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>Charlson comorbidity scoreb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>1.62 (1.46–1.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from endometrial cancer</td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>1.19 (1.06–1.35)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.07 (0.98–1.19)</td>
<td>0.24</td>
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<tr>
<td>Charlson comorbidity scoreb</td>
<td></td>
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<tr>
<td>≥2</td>
<td>1.06 (0.92–1.22)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Adjusted for covariates as shown in Table 1: age (<70, 70–74, 75–79, 80–84, ≥85); year of diagnosis (continuous); tumor stage (FIGO IA/IB/IIA, FIGO IIB/IIB, FIGO IIB/IIIB, unknown); tumor grade (I, II, III, unknown); histologic type (I, II, III, unknown); surgery, radiation, chemotherapy within 1 year of diagnosis (yes or no for each treatment type); census tract median income (quartiles, unknown); census tract education (tertiles, unknown); marital status (married, not married, unknown); geographic area (Northeast, South, Midwest, West); urban residence (metro, nonmetro); prior cancer (yes or no).

bCharlson score excludes diabetes, hypertension, and cancer.
patients in these studies were located by medical record review or took part in case–control studies, resulting in a larger age range than in our study. These studies did not report on the racial composition of their patient groups, but given their locations (Europe, Pittsburgh, or the Midwest) it is likely that they were almost entirely white. One prior study (15) found poorer survival for women with clinical stage I endometrial cancer and severe hypertension.

Insulin and the related insulin-like growth factor (IGF-1) are strongly mitogenic to endometrial tissue (24), providing a biologic rationale for the observation that diabetes is a risk factor for endometrial cancer. Whether diabetes is a risk factor for black women is not established as there are currently no studies of risk factors in black women. In endometrial cancer cell lines, estradiol upregulates IGF-1 to increase proliferation in established tumors in vitro (25), likely leading to more aggressive tumors and poorer outcomes; whether these relationships are the same in blacks and whites is not known. We note that there are other differences between blacks and whites in diabetes-related diseases. For example, the metabolic syndrome is a risk factor for development of diabetes as well as cardiovascular disease. Although blacks are at higher risk of diabetes than whites, they are unlikely to share 2 of the 5 established markers of metabolic syndrome, high triglycerides, and low high-density lipoprotein cholesterol (26). In addition, among patients receiving dialysis for end-stage renal disease, most of whom have an underlying diagnosis of diabetes, blacks have more favorable survival than whites (27). Overall, there is a good deal that is not known about potential racial differences in the biologic effects of diabetes.

The SEER-Medicare database is large, population based, and includes extensive data on disease characteristics, treatment, and demographic characteristics. Because the

![Table 4. Impact of race on survival in women with endometrial cancer](image)

<table>
<thead>
<tr>
<th>Race</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
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<td>Model 1*</td>
</tr>
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<td></td>
<td></td>
<td>Model 2*</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1.86 (1.71–2.04)</td>
<td>1.19 (1.08–1.31)</td>
</tr>
<tr>
<td>Cancer-specific survival</td>
<td>2.18 (1.89–2.51)</td>
<td>1.30 (1.11–1.52)</td>
</tr>
</tbody>
</table>

NOTE: Model 2 further adjusted for diabetes (yes/no), hypertension (yes/no), prior cancers (yes/no), and other comorbid conditions (0, 1, ≥2).

1Model 1 adjusted for covariates as shown in Table 1: age (<70, 70–74, 75–79, 80–84, ≥85); year of diagnosis (continuous); tumor stage (FIGO IA/IB/IIA, FIGO IC/IIB/IIIA, FIGO IIIB-IVB, unknown); tumor grade (I, II, III, unknown); histologic type (I, II, III, unknown); surgery, radiation, chemotherapy within 1 year of diagnosis (yes or no for each treatment type); census tract median income (quartiles, unknown); census tract education (tertiles, unknown); marital status (married, not married, unknown); geographic area (Northeast, South, Midwest, West); urban residence (metro, nonmetro).

Patients in these studies were located by medical record review or took part in case–control studies, resulting in a larger age range than in our study. These studies did not report on the racial composition of their patient groups, but given their locations (Europe, Pittsburgh, or the Midwest) it is likely that they were almost entirely white. One prior study (15) found poorer survival for women with clinical stage I endometrial cancer and severe hypertension.

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The SEER-Medicare database is large, population based, and includes extensive data on disease characteristics, treatment, and demographic characteristics. Because the
median age at diagnosis of endometrial cancer is 62 in white women and 63 in blacks and 58% of women with endometrial cancer are diagnosed before age 65 (2), the results found here among women ages 66 years and older may not be generalizable to all patients with endometrial cancer.

The finding that black women with hypertension had improved overall survival was surprising. Overall, the findings related to hypertension should be interpreted cautiously. Because diabetes and hypertension are primarily treated with outpatient prescription medications, which were not covered by Medicare before 2006, we were unable to identify which women received treatment for these conditions or to determine how well their conditions were controlled.

Because of the strong association of endometrial cancer with overweight and obesity and the association of high body mass index with diabetes and hypertension, we expected relatively high proportions of women with these conditions in this cohort. Twenty-two percent of white women and 41% of blacks met the criteria for diabetes (19). In comparison, the prevalence of diagnosed diabetes was 14% in whites and 28% in blacks in non–Hispanic women aged ≥65 in recent data from National Health and Nutrition Examination Survey (NHANES; ref. 28), based on a question as to whether participants were ever told they had diabetes by a doctor or other health professional. For hypertension, the proportion observed in this cohort, 52% in whites and 73% in blacks, was lower than that observed in recent NHANES data, where among white and black women aged ≥60, about 68% and 84%, respectively, were found to have hypertension based on blood pressure measurements taken during the study examination (29). Our claims based algorithm, requiring 2 claims for hypertension 30 days apart, may have identified only the more serious cases.

Although we did not adjust for the type of hospital where care was received or the type of surgeon, other work using the SEER-Medicare database has shown that blacks are more likely to be treated at NCI-designated cancer centers for endometrial (30) and other cancers (31). Black women with endometrial cancer are also more likely than whites to have surgery conducted by a gynecologic oncologist (30). The reason for this is likely to be that blacks in the SEER-Medicare database are primarily residents of urban areas where they have access to care at NCI cancer centers and by appropriate specialists (30). Including variables related to type of hospital or surgeon would be unlikely to affect our comparisons between racial groups.

Conclusions

In a population-based cohort of older women with endometrial cancer, we found that diabetes was related to poorer disease-specific survival among white women but not among blacks. The disparity between black and white women in both overall and disease-specific survival was not accounted for by presence of diabetes, hypertension, or other comorbid conditions. The differences we found for endometrial cancer–specific survival among white and black women, along with results from clinical trials showing less favorable outcomes for black women (8), provide support for the hypothesis that there are unknown biologic differences between black and white patients that account for the observed disparity in survival from endometrial cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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