Racial Differences in Surgically Staged Patients With Endometrial Cancer

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This study examined whether differences in survival for endometrial cancer attributed to race are primarily associated with socioeconomic status, comorbid illnesses, molecular genetic alterations, and other disease-related characteristics identified as poor prognostic factors. One hundred fifty-two surgically staged patients with endometrial cancer (37 African-American and 115 European-American women) treated from 1990 to 1994 were analyzed for differences in demographics, disease-related characteristics, and survival.

Survival was poorer for African-American women than for European-American women. African-American women had lower socioeconomic status and a higher prevalence of poor prognostic factors. Surgical stage, positive peritoneal cytology, angiolymphatic invasion, cervical stromal involvement, and a history of other malignancies were similar between the two groups. The most important predictors of survival were age at diagnosis, surgical stage, myometrial invasion, positive peritoneal cytology, cervical stromal involvement, tumor grade, aneuploidy, histology, S-phase fraction, number of poor prognostic factors, and race. Racial differences in survival were not explained by socioeconomic status, comorbid illnesses, or estrogen use. When incorporating the number of poor prognostic factors in a survival model with race and surgical stage, race ceased to be of significant prognostic value. In an analysis restricted to women with poor prognostic factors, this phenomena also occurred after adjusting for the number of poor prognostic factors. These findings suggest that the cumulative number of poor prognostic factors, not race, is a more important predictor of survival in endometrial cancer. (*J Natl Med Assoc.* 1997;89:134-140.)

Key words: cancer ◆ endometrial cancer ◆ gynecologic oncology

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Endometrial cancer is the most common gynecologic malignancy in the United States.[1] There are intriguing differences in incidence rates and survival rates related to ethnicity, specifically when comparing African-American and European-American women. European-American women have a higher age-adjusted incidence rate of endometrial cancer of 22.2 per 100,000 compared with 14.6 per 100,000 for African-American women. However, the average age-adjusted mortality rate for African-American women is approximately twice that of European-American women: 6.0 per 100,000 versus 3.3 per 100,000.[2]

The literature consistently shows that African-American women with endometrial cancer have poorer survival rates than European-American women, implying that race is an independent predictor of survival.[3-7] Many studies do not take into account possible confounding variables such as socioeconomic status, comorbid illnesses, and molecular genetic alterations. Further limitations include the use of referral populations and changes in treatment modalities and the surgical staging process over the time interval of study.

This investigation was designed to 1) evaluate differences in demographic and disease-related characteristics at diagnosis; 2) identify important predictors of survival; and 3) determine if differences in survival for endometrial cancer attributed to race are, in fact, primarily associated with differences in socioeconomic status, comorbid illnesses, molecular genetic alterations, and other disease-related characteristics known to be poor prognostic factors.

MATERIALS AND METHODS

Our study base was the defined population of all women receiving their primary medical care within the Henry Ford Healthcare System (HFHS), a large vertically integrated medical care system and group practice that includes primary and specialty care. One hundred fifty-two patients who were diagnosed with endometrial cancer (37 African-American and 115 European-American women) from 1990 to 1994 were identified. All patients who required adjuvant treatment were uniformly treated postoperatively based on their poor prognostic factors.

Data on demographic characteristics, surgical stage, poor prognostic factors (tumor grade, myometrial invasion, peritoneal cytology, cervical stromal involvement, and angiolymphatic invasion), survival status, socioeconomic status, molecular genetic alterations (S-phase fraction and DNA ploidy), and comorbid illnesses were collected. Except for socioeconomic status, the data in this study were obtained from available HFHS databases. Medical records were reviewed to verify database information. Socioeconomic status was measured by income level, which was inferred for each patient based on census block data for the reported residential address.[8]

All patients were staged surgically. However, 16 patients (5 African Americans and 11 European Americans) were noted to have discrepancies in information related to surgical staging between the medical record and the database information; for these individuals, surgical stage was classified as missing. Accurate information on the final grade in the uterine specimen was unavailable for one European-American patient; this patient's grade was classified as missing.

The significance of differences between African-American and European-American women in categorical demographic and disease-related characteristics was assessed using chi-square tests.[9] Survival differences were assessed using the log-rank test to determine significance.[10] Rank-sum tests were used to assess the significance of differences in ordinal and continuous variables between African-American and European-American women.[11] The prognostic value of each of the categorical variables was assessed using log-rank tests, and single-variable proportional hazards models were fitted to continuous variables.[10] In addition, the importance of the number of biological characteristics indicating poor prognosis was assessed; these factors were poorly differentiated lesions (FIGO grade 3), >50% myometrial invasion, papillary serous or clear cell histology, S-phase fraction, cervical stromal involvement, peritoneal cytology, and aneuploidy. Finally, proportional hazards models were fit to those demographic characteristics that had significant prognostic value with each of the disease-related characteristics.[10]

RESULTS

Racial Differences in Demographic and Disease-Related Characteristics

A comparison of crude survival distributions is shown in Figure 1. One-year survival for African-American women was 88% compared with 100% for European-American women. Five-year survival was 68% and 77%, respectively. The difference in survival distributions was significant at $P=.01$.

African-American women tended to have lower incomes ($P<.001$) and a higher prevalence of obesity at diagnosis ($P=.05$) (Table 1). European-American women had a higher prevalence of other malignancies ($P=.02$). The age distributions were similar ($P=.12$), and there were no significant differences in the prevalence of reported hypertension ($P=.33$), diabetes ($P=.44$), heart disease ($P=.73$), stroke ($P=.24$), or pulmonary conditions ($P=.51$), either considered individually or as a group that included obesity ($P=.24$). Estrogen use was low among European-American women (7%) and nonexistent in African-American women; the difference was not statistically significant ($P=.12$).

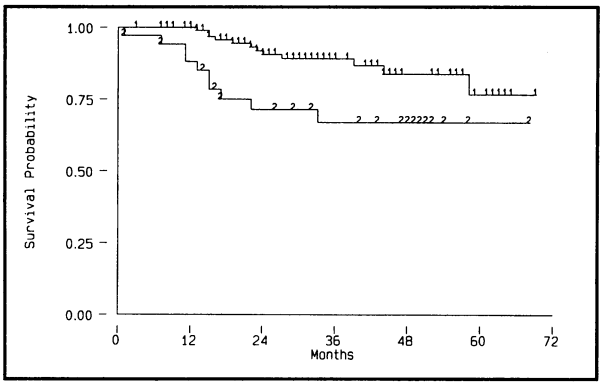

Figure 1.
Survival curves for European-American (1) and African-American women (2). Difference in survival distribution is significant at $P=.01$.

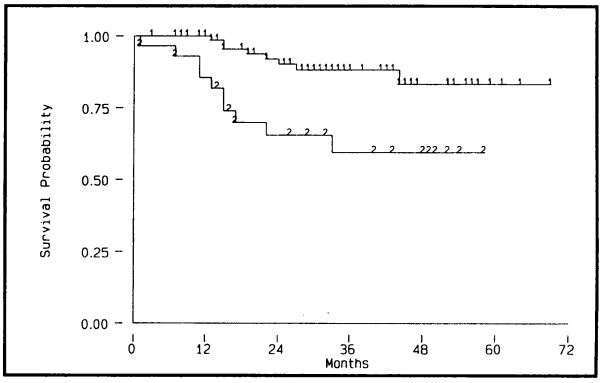

Figure 2.
Survival curves for comparison of European-American women (1) and African-American women (2) with any of the five poor prognostic characteristics. Difference in survival distribution is significant at $P=.002$.

The groups differed, however, with respect to many of the disease characteristics (Table 1). African-American women had a higher prevalence of papillary serous or clear cell histology ($P=.005$), higher grade tumors ($P=.004$), more extensive myometrial invasion ($P=.02$), and a higher S-phase fraction ($P=.003$) than European-American women, but not aneuploidy ($P=.15$). In addition, African-American women tended to have a greater total number of poor prognostic factors than European-American women ($P=.01$); for example, 27% of African-American women had three or more of these factors compared with 12% of European-American women. There was no difference between the race groups in angiolymphatic invasion ($P=.64$), surgical stage ($P=.54$), positive peritoneal cytology ($P=.28$), or cervical stromal involvement ($P=.21$).

Predictors of Survival

Considered one at a time, the most important predictors of survival were disease characteristics: surgical stage ($P<.0001$), myometrial invasion ($P<.0001$), positive peritoneal cytology ($P=.0002$), cervical stromal involvement ($P=.004$), grade in uterine specimen ($P=.008$), aneuploidy ($P=.01$), papillary serous or clear cell histology ($P=.02$), and S-phase fraction ($P=.03$) (Table 2). History of pulmonary disease ($P=.006$) and age at diagnosis ($P=.01$) were also important prognostic characteristics. Income was not prognostic for survival ($P=.25$) nor was the presence of any one of the chronic diseases ($P=.14$).

Each of the disease characteristics were incorporated, one at a time, into a model with race and age at diagnosis (Table 3). Race remained an important predictor of survival in the models with surgical stage, tumor grade, papillary serous or clear cell histology, positive peritoneal cytology, or cervical stromal involvement. Race became an insignificant predictor of survival when either S-phase fraction ($P=.20$) or aneuploidy ($P=.12$) was the disease characteristic.

An exploratory analysis was conducted using women with any one of the five poor prognostic characteristics, and even in this subgroup, African-American women had significantly poorer survival than European-American women ($P=.002$) (Figure 2). Additional analyses were conducted for each of the poor prognostic factors (Table 4). Although racial differences were diminished, they did not completely disappear. However, when comparisons were adjusted for number of poor prognostic factors, race ceased to have significant prognostic value.

A model incorporating number of poor prognostic factors, surgical stage, and race was fitted to the data. Both surgical stage ($P<.001$) and number of poor prognostic factors ($P=.04$) were significant predictors of survival, but race ($P=.08$) was of marginal importance.

DISCUSSION

Our data indicate that African-American women with endometrial cancer have a higher prevalence of poor prognostic factors. Similar findings have been reported in several studies.[3,4,12] Hill et al[12] showed African-American women presented with a higher stage of disease, which they attributed to possible unequal access to care. However, no dif-

Table 1. Differences Between African-American and European-American Women in Demographic and Disease-Related Characteristics

	No. (%) African American (n=37)	No. (%) European American (n=115)	*P* Value
Income >$30,000	10 (27)	82 (79)	<.001
Hypertension	23 (62)	61 (53)	.33
Diabetes	5 (14)	22 (19)	.44
Obesity	21 (57)	44 (39)	.05
Heart disease	8 (22)	28 (24)	.73
Cerebrovascular accident	3 (8)	4 (3)	.24
Pulmonary disease	2 (5)	10 (9)	.51
Any of above chronic diseases	30 (81)	82 (71)	.24
Other malignancies	1 (3)	22 (19)	.02
History of estrogen use	0 (0)	7 (7)	.12
Suspicion of endometrial cancer on Pap smear	12 (63)	28 (44)	.14
Surgical stage			.54
IA	5 (16)	16 (15)	
IB	14 (44)	47 (45)	
IC	3 (9)	12 (12)	
IIA	1 (3)	5 (5)	
IIB	3 (9)	7 (7)	
IIIA	1 (3)	6 (6)	
IIIB	0 (0)	3 (3)	
IIIC	1 (3)	5 (5)	
IVA	3 (9)	1 (1)	
IVB	1 (3)	2 (2)	
Papillary serous or clear cell	10 (30)	11 (10)	.005
Grade in uterine specimen			.004
Well differentiated	8 (24)	57 (54)	
Moderate differentiation	8 (24)	24 (23)	
Poorly differentiated	17 (52)	25 (24)	
Myometrial invasion			.02
Invading <50	25 (76)	78 (73)	
Invading >50	3 (9)	25 (23)	
Extending to serosa	5 (15)	4 (4)	
Aneuploidy	12 (50)	26 (34)	.15
S-phase fraction >5%	21 (100)	49 (74)	.01
Positive peritoneal cytology	5 (17)	10 (10)	.28
Cervical stromal involvement	7 (21)	13 (12)	.21
Angiolymphatic invasion	6 (19)	16 (15)	.64
No. of poor prognostic factors			.01
0	6 (16)	33 (29)	
1	12 (32)	47 (41)	
2	9 (24)	21 (18)	
3	4 (11)	11 (10)	
4	4 (11)	2 (1)	
5	2 (5)	1 (1)	
Median age at diagnosis (years)	66	64	.12
Median weight (kg)	94	80	.06
Median income	$23,203	$37,240	<.0001
Median S-phase fraction (%)	11	8	.003

Table 2. Predictors of Survival*

Predictor	*P* Value
Race	.01
Age at diagnosis	.01
Weight	.56
Income	.25
Income >$30,000	.65
Hypertension	.49
Diabetes	.67
Obesity	.52
Heart disease	.06
Cerebrovascular accident	.77
Pulmonary	.006
Any of above chronic diseases	.14
Other malignancies	.44
History of estrogen use	.80
Suspicion of endometrial cancer on Pap smear	.21
Surgical stage	<.0001
Papillary serous or clear cell	.02
Grade in uterine specimen	.008
Myometrial invasion	<.0001
Aneuploidy	.01
S-phase fraction (%)	.03
S-phase fraction >5%	.60
Positive peritoneal cytology	.0002
Cervical stromal involvement	.004
Angiolymphatic invasion	.17
No. poor prognostic factors (0 to 5)	<.0001

*Unadjusted for other predictors of survival.

Table 3. Selected Prognostic Factors Adjusted for Age at Diagnosis and Race

	Hazard Ratio	*P* Value	95% CI
Surgical stage	1.7	<.001	1.3 to 2.1
Age at diagnosis	1.1	.02	1.0 to 1.1
African American	4.5	.007	1.5 to 13.6
Papillary serous or clear cell	2.3	.10	0.9 to 6.4
Age at diagnosis	1.0	.03	1.0 to 1.1
African American	2.8	.04	1.1 to 7.4
Grade in uterine specimen	1.7	.08	0.9 to 3.0
Age at diagnosis	1.0	.05	1.0 to 1.1
African American	2.7	.05	1.0 to 7.1
Myometrial invasion	2.7	.01	1.3 to 5.9
Age at diagnosis	1.1	.02	1.0 to 1.1
African American	2.6	.06	1.0 to 7.0
S-phase fraction (%)	1.1	.05	1.0 to 1.2
Age at diagnosis	1.1	.02	1.0 to 1.1
African American	2.1	.20	0.7 to 6.8
Aneuploidy	3.4	.05	1.0 to 11.4
Age at diagnosis	1.1	.08	1.0 to 1.1
African American	2.5	.12	0.8 to 7.7
Positive peritoneal cytology	16.4	<.001	3.9 to 68.1
Age at diagnosis	1.1	<.001	1.1 to 1.2
African American	3.4	.03	1.1 to 10.1
Cervical stromal involvement	3.1	.03	1.2 to 8.2
Age at diagnosis	1.1	.02	1.0 to 1.1
African American	2.6	.04	1.0 to 6.8

*Abbreviations: CI=confidence interval.

ference in stage at diagnosis between African-American and European-American women was found. This may be explained by the fact that all of our subjects were part of a defined population served by a vertically integrated healthcare system and therefore had an identified primary health-care provider and similar access to health-care specialists. In addition, the patients in our study were similar in prevalence of chronic diseases. Liu et al[4] found no difference in the interval of treatment, defined as the beginning of abnormal uterine bleeding to hysterectomy, between African-American and European-American women. However, African-American women presented with more advanced stage disease. The authors provided no information related to comorbid illnesses. Our findings of no difference in stage of disease at diagnosis between African-American and European-American women also may be a reflection of our utilization of a uniform system of staging. All of our patients underwent surgical staging as recommended in 1988 by the International Federation of Gynecology and Obstetrics.[13] Surgical staging was not used on all patients in the other studies.[3,4,12]

Liu et al[4] and Hill et al[12] reported significantly higher estrogen use among European-American women than African-American women. This finding was thought to explain the low prevalence of poorly differentiated lesions in European-American women and the high prevalence of such lesions among African-American women. Our data revealed no statistical difference between African-American and European-American women related

Table 4. Survival Differences Between African-American and European-American Women, Adjusting for Number of Poor Prognostic Factors

	Unadjusted		Adjusted	
	Hazard Ratio for AA	*P* Value	Hazard Ratio for AA	*P* Value
Analysis restricted to women with:				
Papillary serous or clear cell histology	6.7	.08	4.6	.17
Poorly differentiated lesions	3.6	.06	3.2	.09
Myometrial invasion >50%	6.4	.04	2.2	.44
Aneuploidy	3.4	.10	1.7	.47
S-phase fraction >5%	3.3	.05	2.0	.30

Abbreviations: AA=African American.

to a history of estrogen use (P=.12). Despite this finding, African-American women still had a much higher prevalence of poorly differentiated lesions.

Our finding of poorer survival among African-American women with endometrial cancer is consistent with other reports in the literature.[2-7] However, to our knowledge, this is the first report that evaluated survival differences between African-American and European-American women with endometrial cancer in a defined stable population, with all patients having relatively equal access to care and having undergone surgical staging and uniform treatment. Nevertheless, there was still a survival advantage for European-American women diagnosed with endometrial cancer.

Comorbid illness (chronic disease) was evaluated to determine if it affected racial differences in survival. There was no difference in prevalence of comorbid illnesses between the two groups (P=.24), and comorbid illnesses were not a statistically significant predictor of survival (P=.14).

Racial differences in survival also were not explained by differences in estimated income (socioeconomic status). Although income was not a statistically important predictor of survival (P=.25), it was noted to be significant as it related to demographic differences between the two groups ($P\leq$.0001). To critically assess the impact of income on racial differences in survival, income was placed into a survival model with three significant predictors of survival (surgical stage, age at diagnosis, and race). Income did not diminish the prognostic significance of race, which remained a significant predictor of survival (P=.009).

We evaluated if race was a significant predictor of survival in a model that consisted of age at diagnosis and seven disease characteristics known to be significant predictors of survival. African-American race was found to have the highest predictive value of survival (P=.007) in the model when surgical stage was the disease characteristic. This would indicate that an African-American woman has a 4.5 times greater chance of dying from endometrial cancer at the same stage and age as an European-American woman with endometrial cancer. It appears that this phenomenon exists because at a particular stage, multiple poor prognostic factors may coexist. For example, an African-American woman with a stage I-C endometrial cancer also could have up to five poor predictors of survival (poor prognostic factors): a grade 3 lesion, papillary serous tumor, deep myometrial invasion, high S-phase fraction, and aneuploidy. This model gives an example of the strong intermingling and tight association of these poor predictors of survival.

By using the same survival model but incorporating the number of poor prognostic factors, African-American race was no longer statistically significant, indicating that race is not an independent significant predictor of survival. Instead, the number of coexisting poor prognostic factors is a more significant predictor of survival. Although they did not evaluate racial differences, Kadar et al[14] showed similar findings indicating that the number of tumor-related risk factors was the best predictor of survival.

Liu et al[4] found that race was a significant poor prognostic factor even after individually correcting for grade, myometrial invasion, histological types, and lymph node status ($P\leq$.05), but race was not a significant poor prognostic factor after correcting

for stage. Our data differed in the categories of poor prognostic factors evaluated. Nonetheless, except for myometrial invasion, race remained a significant predictor of survival in each category. However, after adjusting for the number of poor prognostic factors, race ceased to have significant prognostic value in each category.

In the survival model incorporating S-phase fraction or aneuploidy as the disease characteristic, race was not a significant predictor of survival. This may indicate that perhaps it is the molecular aspects of the disease that account in part for racial differences in survival. It would seem logical that a pertinent next step would be to explore if there are differences as it relates to alterations in oncogenes, tumor suppressive genes, or DNA repair genes.

The prevalence of poor prognostic factors was unequivocally more common among the African-American women in our study. This finding may be related to underlying biological differences or cultural differences manifested in factors such as diet or other unexplained environmental or lifestyle characteristics that are different between African-American and European-American women. Risk factors such as these can only be identified by well-developed epidemiologic studies.

Limitations of our study are principally related to power, follow-up time, and method of determining socioeconomic status. Based on the number of patients and the proportion who were African-American, we had statistical power of 0.73 to detect differences in 5-year survival of 70% in African-American and 80% in European-American women. Median follow-up was relatively short–31 months for European-American and 43 months for African-American women. Although follow-up time was short, there were no statistical differences between the two groups (P=.15). Finally, census block data is only a surrogate for actual income, and income alone probably is not the best measure of socioeconomic status. However, this method of inference was used consistently for all subjects in our analyses.

CONCLUSIONS

This study has shown that racial differences in survival in our population cannot be explained by unequal access to care, varying treatment modalities, estrogen use, comorbid illnesses, or socioeconomic status. We present models of personal and disease-related variables as predictors of survival in which race was not found to be a statistically significant predictor. While other unmeasured racially related factors may still play a role, these findings suggest that survival differences between African-American and European-American women with endometrial cancer are largely related to differences in the cumulative number of poor prognostic factors between the two groups.

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