Association of African-American Ethnic Background With Survival in Men With Metastatic Prostate Cancer

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Background: African-American men have earlier onset of prostate cancer, higher prostate-specific antigen (PSA) levels, more advanced stage at diagnosis, and higher mortality than white men. It is not known whether the poorer survival of African-American men with prostate cancer reflects their later stage at diagnosis or differences in the basic biology of their disease. To evaluate this question, we examined outcomes of African-American and white men with metastatic prostate cancer in the context of a randomized clinical trial. Methods: Southwest Oncology Group Study 8894 was a randomized phase III trial that compared orchiectomy with or without flutamide in men with metastatic prostate cancer. Using data from 288 African-American and 975 white men in the trial, we conducted a proportional hazards regression analysis to determine if ethnicity was an independent predictor of survival. All statistical tests were two-sided. Results: African-American men were more likely than white men to have extensive disease and bone pain and had poorer performance status, younger age at study entry, higher Gleason score, and higher PSA levels. After adjustment for these prognostic variables, the hazard ratio (HR) for all-cause mortality for African-American men relative to white men was 1.23 (P = .018). Further adjustment for initial quality-of-life assessments also resulted in higher HRs associated with African-American ethnicity relative to white ethnicity (HR = 1.39; P = .007). Conclusions: African-American men with metastatic prostate cancer have a statistically significantly worse prognosis than white men that cannot be explained by the prognostic variables explored in this study. These data should give increased impetus for efforts to detect the disease early in African-American men and for the development of more effective therapies based on potential biologic differences in this ethnic group. [J Natl Cancer Inst 2001; 93:219–25]

The mortality of African-American men 40–60 years of age from prostate cancer is almost threefold greater than that of white men of the same age (1). Overall, black men in the United States have a 47% higher incidence of prostate cancer than white men in the United States and a 128% higher mortality rate from the disease (2). Although it has been suggested that the more advanced stage at diagnosis in African-Americans reflects inequities in education and access to health care, a study in Connecticut (3) suggested that, even in census tracts with similar income levels, African-American ethnic background confers a greater risk of diagnosis with advanced disease.

The poorer prognosis for African-American men could reflect the later stage of diagnosis—and, consequently, poorer prognostic features of the disease—in these men, or it could reflect a biologic difference in the disease. Evidence in favor of the first possibility is provided by several studies that have suggested that survival among men with advanced prostate cancer is similar in the two ethnic groups. However, these studies suffered from small sample size or from uncontrolled variables, such as type of treatment or patient characteristics (4,5).

We (6) published results of Southwest Oncology Group (SWOG) Study 8894 (Intergroup Study 0036), a randomized,
prospective phase III trial comparing orchiectomy with an antiandrogen (flutamide) with orchiectomy and placebo in men with metastatic carcinoma of the prostate. This trial was disappointing in that the addition of flutamide improved survival by only 3 months, an insubstantial difference according to initial trial design assumptions. However, because the trial was planned to accrue a substantial number of African-American men, it provided an opportunity to reanalyze the difference in survival among men with metastatic disease by ethnic background within a rigidly controlled treatment regimen. The large sample size and the lack of uncontrolled variables made this trial a good setting for evaluating whether differences in survival between African-American men and white men can be explained by differences in prognostic variables or whether there may be a difference in the biologic activity of metastatic prostate cancer in African-American men.

**Subjects and Methods**

**Participants**

SWOG Study 8894 (Intergroup Study 0036) enrolled patients with histologically confirmed adenocarcinoma of the prostate, with evidence of metastatic (bone or soft-tissue) disease, and with an SWOG performance status of 0–3 (definitions: 0, fully active; 1, restricted in strenuous activity but ambulatory; 2, ambulatory and capable of self-care but unable to work; and 3, capable of only limited self-care and confined to a bed or chair >50% of the time). Patients with a performance status of 3 were eligible only if pain was the cause of their functional impairment. Patients also had to have adequate renal and hematologic functions. The study was a double-blind, randomized trial. All patients underwent bilateral orchiectomy and were subsequently randomly assigned to receive either flutamide (250 mg three times daily) or a similar-appearing placebo given with the same regimen. Upon progression of the disease, patients on the placebo arm were given the option to crossover to flutamide. The primary endpoint of the study was death from any cause, with a secondary endpoint being progression-free survival. It was determined that a sample size of 1248 patients would achieve 90% power for the primary endpoint, with an overall probability of a type I statistical error of 0.05. This calculation assumed a median survival of 28.3 months in the placebo group (based on the previous SWOG phase III study of luteinizing hormone-releasing hormone agonist therapy with or without flutamide), a hazard ratio (HR) for death from prostate cancer of 0.80 for the flutamide group compared with the placebo group, an accrual rate of 40 patients per month, and a 2-year follow-up period following completion of accrual.

Before orchiectomy, all patients underwent a medical history and physical examination, complete blood cell count, and analysis of serum creatinine, liver enzymes, alkaline phosphatase, acid phosphatase, serum testosterone, and prostate-specific antigen (PSA). Physical examinations and blood analyses were repeated 1 and 3 months later and every 3 months thereafter. Patients underwent chest x-ray, bone scan, bone radiography, and computed tomography of the abdomen and pelvis at study entry and at 6-month intervals for the first 2 years. After the initial 2-year period, radiologic studies (at a minimum, a bone scan) were done if the PSA level rose by more than 25 ng/mL during any 3-month period. All patients were followed until death. Tumor grading by use of the Gleason grading system was accomplished through central pathologic review of biopsy specimens obtained before entry in the study.

Patients were also administered a comprehensive battery of quality-of-life (QOL) assessments (7) at study entry and 1, 3, and 6 months later. In brief, patients completed a SWOG QOL questionnaire that included four areas of general functioning: 1) the Short Form (SF)-36 (SF-36) Physical Functioning Scale (range of possible values = 0–100); 2) the SF-36 Mental Health Index (emotional functioning, possible range = 0–100); 3) the SF-20 Role Functioning Scale; and 4) the SF-36 Social Functioning Scale. The last two scales were not used in the covariate-adjusted analyses in this report, both because they were not primary endpoints in the original study and because they were considered not to be as strongly associated with survival and disease status as the first two scales. The Symptom Distress Scale (possible range = 11–55) was also included in the QOL instrument as a measure of general symptom status; higher scores reflect a worse symptom status. Two global QOL questions were also used in QOL assessments in this report because we hoped that they might add important information about disease severity and morbidity that might not otherwise be captured in the standard disease variables, such as extent of disease, Gleason score, and bone pain. These QOL questions were as follows: 1) “In general, would you say your health is: 1 = excellent, 2 = very good, 3 = good, 4 = fair, or 5 = poor?” and 2) “Score how you feel your life has been affected by the state of your health (any disease or treatment) during the last week: 1 = extremely unpleasant, 2 = unpleasant, 3 = moderately unpleasant, 4 = slightly unpleasant, or 5 = normal (no change).” Because the QOL companion study for SWOG 8894 did not begin until halfway through the accrual period, baseline forms were available for approximately half of the study participants. During the period from December 15, 1989, to September 15, 1994, a total of 1387 patients were randomly assigned to receive either flutamide (700 patients) or placebo (687 patients) after undergoing bilateral orchiectomy. Two thirds of these patients came from 99 SWOG institutions located in 30 states, and the other one third came from Eastern Cooperative Oncology Group institutions. Of the 1387 patients in SWOG 8894, 1286 were eligible for the treatment protocol; therefore, only these patients were used in this reanalysis of survival by race, which included 288 African-Americans, 975 whites, and 23 “other.” However, the patients in whom race was categorized as “other” were excluded from the analysis, leaving a total of 1263 patients.

The median follow-up time for the African-American men in the reanalysis of SWOG 8894 was 5.5 years (range = 4.1–9.3 years, disregarding two patients lost to follow-up in the first 3 months). The median follow-up time for the white men was 6.7 years (range = 3.8–9.3 years). There was no indication of differential loss to follow-up between the two ethnic groups.

All patients gave written informed consent prior to study entry. A separate consent was not obtained for this retrospective analysis. Registering institutions were required to provide proof that their Institutional Review Board had reviewed and approved the study protocol within the previous calendar year in order to be eligible to register patients.

**Statistical Analysis**

All covariates that were available from this clinical trial with less than 15% missing values and that were thought to be predictive of survival were included in the covariate-adjusted analyses. Regardless of significance level, all covariates were kept in the adjusted model. The covariates used in the analysis included ethnicity (African-American versus white), PSA concentration (ng/mL) as a continuous variable that was then divided by 100 to make the HR more clinically interpretable (i.e., the additional risk of death for every 100-unit increase of PSA), presence of bone pain (yes versus no), age as a continuous measure divided by 5 for a more interpretable HR estimate (i.e., the additional risk of death for every 5-year increase in age), extent of disease (extensive versus minimal), Gleason score category (= 5, 6–7, or 8–10), and SWOG performance status (2–3 versus 0–1). Information on each of these covariates was collected at the time of study entry. Missing values for the covariates at study entry were noted in 0%, 10%, 13%, 0%, 0%, 11%, and 0% of patients, respectively. Of the 1263 men in the study, 916 (198 of the 288 African-Americans, or 69%, and 718 of the 975 whites, or 74%) had complete values for all of the covariates. A review of the missing values found no association of any missing value with ethnicity. In an additional analysis that included QOL measures as covariates, a square-root transformation was used for the physical functioning, emotional functioning, and symptom distress scales because of skewed distributions. The global QOL and general health status variables were included in the model as ordinal variables with a possible range of 1–5.

All proportional hazards models were fit with the use of the PHREG procedure in the SAS software (SAS Institute, Inc., Cary, NC) (8). The Wald chi-square test was used to evaluate the contribution of each covariate in the multivariate model. The proportional hazards assumption was evaluated in SPLUS, with the use of Shoenfeld residuals in a global test of proportional hazards (9). Interactions of covariates with ethnic group were evaluated by assessment of the score statistic for each univariate interaction in the covariate-adjusted model. The addition of ethnicity to the covariate-adjusted model was evaluated in the following manner: The −2 log likelihood for the covariate-adjusted model was evaluated in the following manner: The −2 log likelihood for the covariate-adjusted model (without ethnicity) was obtained from fitting the model. A second model was then fit that included the same covariates but with the addition of an indicator for African-American men. The −2 log likelihood was obtained for this second model. The difference in these −2 log likelihoods is the likelihood ratio test, which evaluates whether ethnicity provides a statistically significant contribution above and beyond the
covariates already in the model. This chi-square test has 1 df.

The LIFETEST procedure from SAS was used to perform the stratified log-rank test (8). Bone pain, performance status, and extent of disease were included in the model under the STRATA statement. Ethnicity was then specified in the TEST statement.

All statistical tests were two-sided.

RESULTS

No differences were noted in treatment assignment by ethnicity, with 49.3% of the African-American men and 50.2% of the white men randomly assigned to receive flutamide. A comparison of several parameters that reflect the extent of disease at diagnosis and have the potential to affect survival (Table 1) shows that, compared with the white men in the study, the African-American men in the study were generally younger, had higher PSA levels, had more extensive disease, had higher Gleason scores, had more frequent bone pain, and had a worse performance status.

African-American men in the study also had poorer survival than the white men in the study, perhaps because of their later stage at diagnosis. Of the 198 African-American and 718 white men for whom complete information about covariates was available at study entry, the median survival was 26 months and 35 months, respectively (log-rank test (8)). No differences were noted in treatment assignment by ethnicity, with 49.3% of the African-American men and 50.2% of the white men randomly assigned to receive flutamide. A comparison of several parameters that reflect the extent of disease at diagnosis and have the potential to affect survival (Table 1) shows that, compared with the white men in the study, the African-American men in the study were generally younger, had higher PSA levels, had more extensive disease, had higher Gleason scores, had more frequent bone pain, and had a worse performance status.

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An unadjusted proportional hazards regression analysis of survival provided an estimated HR for mortality in African-American men relative to white men of 1.38 (95% confidence interval [CI] = 1.17 to 1.64). If the 347 patients for whom at least one covariate was missing were included in the regression analysis, the HR remained essentially the same.

To determine whether the poorer survival among African-American men relative to white men was a reflection of their poorer prognostic factors, we controlled for the effect of these factors in a multivariate proportional hazards regression model (Table 2). As indicated by HR estimates that are greater than 1, the predictors of poor survival among all patients, in order of strength, were extensive disease, worse performance status, high Gleason score, and presence of bone pain. In contrast, protocol treatment assignment, subject age, and PSA levels at study entry did not have a statistically significant predictive effect on overall survival among African-American and white patients after adjustment for the other predictors in the model. PSA level was a statistically significant predictor of overall survival in the univariate model (data not shown) but not in the multivariate model (Table 2). Protocol treatment and age were not statistically significant even in the univariate model (data not shown). After adjustment for the potentially confounding variables, the African-American patients had an HR for death relative to white patients of 1.23.
(95% CI = 1.04 to 1.47), and this increased risk was statistically significant (P = .018). The likelihood ratio test for the addition of ethnicity to the model with the other prognostic variables showed that the effect of ethnicity was statistically significant (chi-square = 5.40 with 1 df; P = .02).

To test the robustness of the results from the covariate-adjusted proportional hazards regression model, we employed the stratified log-rank test to evaluate whether the survival distribution of African-Americans was equivalent to that of whites, stratifying on eight prognostic groups. We chose this test because it required fewer assumptions than the covariate-adjusted proportional hazards model. The eight strata were defined by bone pain (yes versus no) × extent of disease (extensive versus minimal) × Gleason score (≥8 versus <8) because these were the strongest predictors in Table 2. The results of the stratified log-rank test also supported the conclusion that African-American men have a worse survival relative to white men (P = .007).

To determine whether the potential predictors in the covariate-adjusted model described in Table 2 had the same association with survival for African-Americans and whites, we performed an evaluation of interactions. For example, it might be hypothesized that PSA level at study entry would better predict survival in one ethnic group over the other. However, the results of tests of interactions of covariates (specifically, treatment arm, presence of bone pain, performance status, extent of disease, Gleason score, and PSA level at randomization) with ethnic background were not statistically significant (all P values >.40), indicating that these covariates have the same general effect on survival for both ethnic groups.

To further explore the possible impact of other variables on the differences in survival between ethnic groups, we performed a proportional hazards regression analysis to evaluate the impact of self-reported QOL measures at study entry. A smaller number of patients (i.e., 486 white and 114 African-American) had complete data for this analysis. This regression analysis incorporated results of global QOL and general health assessments (Table 3). (For the global QOL measure, high scores indicate better perceived quality of life; for the general health measure, low scores indicate better perceived health.) Disease extent, presence of bone pain, Gleason score of 8–10, and the general health status measures all were statistically significant, independent predictors of overall survival. After adjustment for these measures, African-American ethnicity continued to be associated with a statistically significantly higher risk of death (HR = 1.39; P = .007).

A second, similar proportional hazards regression analysis incorporated three self-reported QOL scales, covering emotional function, physical function, and symptom distress (Table 4). (For the emotional and physical function scales, higher scores reflect better function, whereas higher scores on the symptom distress scale reflect worse symptoms.) The same clinical variables listed in the previous paragraph and the patient report of physical function were also statistically significant predictors of survival. Again, after adjustment for differences in quality of life as assessed by these scales, African-American ethnicity was associated with a statistically significantly higher risk of death (HR = 1.42; P = .004). Evaluation of the proportional hazards assumption for each of the covariate-adjusted models specified in Tables 2–4 indicated a reasonable fit to the data, whereas the unadjusted model with only an indicator for African-American versus white did not seem to fit the data well.

**DISCUSSION**

There is unequivocal evidence that African-American men are disproportionately affected by carcinoma of the prostate. They develop it at an earlier age (manifesting a higher PSA level than their white counterparts at a given age), present with the disease at a more advanced stage, are more likely to be diagnosed with the disease, may be less likely to respond to treatment for cure, and are more likely to die of the disease (10,11). At issue is why. Is it that issues of health care access or health behaviors result in later diagnosis in African-Americans, or is it that the disease behaves intrinsically differently in African-Americans than in whites?

A large body of literature suggests that patterns of care and health behaviors may affect outcomes of prostate cancer in African-American men. For example, although increasing evidence suggests that...
Table 4. Multivariate proportional hazards model results for all-cause mortality among the 486 African-American and white patients for whom complete information about covariates was available, including information from three quality-of-life subscales: emotional function, physical function, and symptom distress*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR (95% CI)†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease, extensive versus minimal</td>
<td>1.60 (1.20 to 2.12)</td>
<td>.001</td>
</tr>
<tr>
<td>Performance status, 2–3 versus 0–1§</td>
<td>1.04 (0.76 to 1.42)</td>
<td>.80</td>
</tr>
<tr>
<td>Bone pain, presence versus absence</td>
<td>1.30 (1.03 to 1.65)</td>
<td>.029</td>
</tr>
<tr>
<td>Treatment arm, flutamide versus placebo</td>
<td>0.88 (0.71 to 1.07)</td>
<td>.20</td>
</tr>
<tr>
<td>PSA level in ng/mL, additional risk of death for every 100-unit increase in PSA level</td>
<td>1.00 (0.99 to 1.01)</td>
<td>.82</td>
</tr>
<tr>
<td>Age, y, additional risk of death for every 5-y increase in age</td>
<td>1.02 (0.96 to 1.09)</td>
<td>.55</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>1.00 (reference level)</td>
<td></td>
</tr>
<tr>
<td>6–7</td>
<td>1.08 (0.71 to 1.62)</td>
<td>.73</td>
</tr>
<tr>
<td>8–10</td>
<td>1.74 (1.17 to 2.57)</td>
<td>.006</td>
</tr>
<tr>
<td>Emotional function, additional risk of death for every 1-unit increase in the square-root measure of the score</td>
<td>1.07 (0.99 to 1.16)</td>
<td>.077</td>
</tr>
<tr>
<td>Physical function, additional risk of death for every 1-unit increase in the square-root measure of the score</td>
<td>0.92 (0.87 to 0.97)</td>
<td>.002</td>
</tr>
<tr>
<td>Symptom distress, additional risk of death for every 1-unit increase in the square-root measure of the score</td>
<td>1.21 (0.99 to 1.47)</td>
<td>.060</td>
</tr>
<tr>
<td>Ethnicity, African-American versus white</td>
<td>1.42 (1.12 to 1.81)</td>
<td>.004</td>
</tr>
</tbody>
</table>

*HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.
†Each HR and P value was adjusted for all of the other factors in the model.
‡P values are based on the Wald chi-square test and are two-sided.
§Performance status: 0, fully active; 1, restricted in strenuous activity but ambulatory; 2, ambulatory and capable of self-care but unable to work; and 3, capable of only limited self-care and confined to a bed or chair more than 50% of the time.
¶A higher value indicates more favorable function.
†A lower value indicates less distress.

early diagnosis may affect mortality from the disease. African-American men may be less likely than white men to participate in early detection programs (12). Traditional mass-advertising methods to attract men to such programs may not function as well in the African-American male community as offering early detection programs at work or at church or through peer testimonials (13–15). In addition, literacy among African-American men may play a role in participation in early detection practices (16). Bennett et al. (16), studying African-American and white men in Chicago, IL, and in Shreveport, LA, found that African-American men were statistically significantly more likely to present with advanced disease than were white men (49% versus 36%) but that this difference disappeared after adjustment for literacy levels. African-American men in these two populations were statistically significantly more likely than white men to have literacy levels lower than those of the sixth grade. This observation may help explain the finding that, among men in a large group of counties in North Carolina, fewer than one third of both African-American and white men were aware that African-American men were at a higher risk of prostate cancer (17).

The outcomes of treatment for African-American and white men have been compared in various populations in an attempt to correct for a second variable that may affect outcomes, i.e., access to health care. The results have been conflicting. In the Department of Defense health care beneficiary population, Optenberg et al. (5) previously demonstrated equivalent outcomes in this population, which has equal access to health care. Fowler and Terrell (18) found similar results in a sample of the Department of Veterans Affairs population. Conversely, Robbins et al. (19), studying the California Kaiser-Permanente population, found statistically significantly worse outcomes among African-Americans, even after adjusting for age and stage of the disease. However, they observed no difference between ethnic groups among patients with metastatic disease. One explanation for the differences in outcome between African-Americans and whites that may also reflect a difference in access to health care was suggested by a study of Medicare beneficiaries in New York State (20). Among men older than 65 years in this population, African-Americans were less likely to receive radical prostatectomy than white men. This difference has been reported as well in two reviews of the U.S. experience as documented by the Surveillance, Epidemiology, and End Results (SEER) Program (21,22).

However, all of these previous comparisons of the nature of prostate cancer in African-American and white men have been observational and were, therefore, unable to control for any number of variables. In our review of the outcomes of treatment of metastatic prostate cancer in African-American and white men, we had the distinct advantage of being able to make comparisons within the context of a randomized, prospective trial—a circumstance that minimizes many of the biases attendant with observational studies. One of the most important qualities of a review of these data from this trial is that patient care was provided in a rigidly prescribed fashion through a study protocol that provided guidance on clinical follow-up as well as follow-up schedule. An additional advantage of an analysis within a randomized clinical trial was that the medical treatment provided to each patient was designed to be identical, with the exception of the drug treatment differences in the two study arms. An analysis of major study deviations, such as a patient refusing his assigned treatment or the treatment modality never being administered, in SWOG 8894 revealed that such deviations occurred in just 1.4% of white men and 3.8% of African-American men. An additional important attribute of our study was the robust nature and the high quality of the data gathered in each patient, including comprehensive measures of quality of life, which allowed for subsequent regression analysis on these potentially predictive variables and a better understanding of the effect of ethnic background on treatment outcomes.

Our central observation was that there is indeed a fundamental difference in the outcome of treatment of metastatic prostate cancer in African-American men than in white men and that African-Americans have statistically significantly inferior outcomes, even after we controlled for their poorer prognostic variables. Again, we must ask the question: why? Although access to health care and education and
than in white men. Moreover, genetic variants in the HSD3B2 gene—whose product, type II 3β-hydroxysteroid dehydrogenase, plays a role in the inactivation of dihydrotestosterone (DHT), thereby potentially decreasing intraprostatic androgen stimulation from DHT—are much more common in African-American men than in white men. Moreover, genetic variants in the HSD3B2 gene—whose product, type II 3β-hydroxysteroid dehydrogenase, plays a role in the inactivation of dihydrotestosterone (DHT), thereby potentially decreasing intraprostatic androgen stimulation from DHT—are much more common in African-American men than in white men (25).

Further support for the possibility that African-Americans and whites differ in the hormonal milieu in the prostate was provided by a study of serum samples from a large group of African-American, white, and Asian men from California, Hawaii, and Vancouver, Canada (26). Although serum testosterone levels were highest in Asian men, intermediate in white men, and lowest in African-American men, the ratios of DHT to testosterone were highest in African-Americans, intermediate in whites, and lowest in Asians. The authors speculated that such ethnic differences could result from differences in the activity of 5α-reductase in these ethnic groups. In support of this concept is the finding that some polymorphic variants of the SRD5A2 gene (which codes for type II steroid 5α-reductase) are found more commonly in African-American men than in white men (27).

Another possible biologic difference between African-American men and white men that could result in an intrinsic difference in prostate cancer outcome is the number of repeats of the polymorphic CAG and GGC microsatellite sequences in exon 1 of the androgen receptor gene. The length of these repeats has been demonstrated to be related to androgen sensitivity (28). In addition, Irvine et al. (29) studied three groups of men (45 African-American, 39 non-Hispanic white, and 39 Asian men) and found the prevalence of short CAG repeats (<22 repeats) to be highest (75%) in African-American men, intermediate (62%) in non-Hispanic white men, and lowest (49%) in Asian men. Other researchers (30) have found polymorphisms of the vitamin D receptor gene that may also play a role in more aggressive disease among African-American men.

Although we conducted our analysis within the context of a randomized, prospective trial and we analyzed and controlled for multiple variables, other variables were almost certainly not measured (and perhaps cannot be measured) that may play a role in the difference in survival between African-American men and white men with metastatic prostate cancer. A study that is designed to specifically address the differences in mortality between the two ethnic groups and that incorporates all available prognostic variables is necessary for the question of the source of these differences to be better answered. Even then, it would not be possible to control for variables that have not yet been identified. Nevertheless, the degree of difference in outcomes in our analysis remains remarkable after controlling for variables previously identified as of importance to mortality. It is possible that adjusting for variables such as the Gleason score could be argued to be “overadjusting” the model because tumor grade could be a pathologic feature of prostate cancer that varies with ethnic background. Indeed, when the Gleason score was removed from the covariate-adjusted model, the difference in survival between African-American men and white men was even more pronounced (HR = 1.35; 95% CI = 1.14 to 1.59). This result suggests that the survival difference between the two ethnic groups could be even larger than what is stated in the “Results” section (HR = 1.23) if one believes that the Gleason score is influenced, at least in part, by ethnicity.

The implications of our observation of the differences in prostate cancer outcomes in African-Americans and whites, considered in the context of the body of evidence already available, are profound. First, socioeconomic issues, including education, financial resources, and health care-seeking behaviors, almost certainly play a role in the greater impact of prostate cancer in African-American men. These issues, although major obstacles to optimal health care outcomes, are surmountable with interventions such as education, better access to health care, and culturally sensitive early-diagnosis programs. More challenging, however, is how best to approach the potential difference in biologic behavior of the disease. Certainly, the best, albeit crude, approach at this time is to encourage early diagnosis at an earlier age in African-American men. Given the higher PSA levels and more aggressive disease seen in African-Americans at every age, this approach is a rational outgrowth of current data. However, our findings and those of others suggest that efforts should be directed to culling through the potential biologic differences (e.g., in the androgen receptor, vitamin D receptor, retinoic acid receptor, and various enzymes controlling androgen metabolism) found between African-American men and white men. As more effective adjuvant therapies are developed, consideration must be given to providing these therapies to African-Americans, men who may be at a greater risk of treatment failure and disease progression.

In summary, our review of the outcomes of men with metastatic prostate cancer treated in the context of a randomized, prospective phase III trial of orchidectomy with and without flutamide for metastatic prostate cancer has shown that African-American men are at a statistically significantly greater risk of death following hormonal therapy for advanced prostate cancer. This difference persisted after we controlled for other variables known to predict survival and outcomes of therapy. These data suggest the existence of ethnicity differences in the biology of the disease and should prompt further investigations into the identification of the causes of this difference and subsequent development of more effective therapies.

REFERENCES

(5) Optenberg SA, Thompson IM, Friedrichs P, Wojcik B, Stein CR, Kramer B, Race, treatment and long-term survival from prostate can-


Notes

1Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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