BLACK-WHITE DIFFERENCES IN SURVIVAL FROM LATE-STAGE PROSTATE CANCER

Objective: To examine differences between African Americans (Blacks) and non-Hispanic Whites in risk of death after diagnosis of later-stage prostate cancer in a large sample of patients from US population-based cancer registries. The theory that Black patients with advanced cancer have a lower survival rate compared to their White counterparts, based on a single clinical trial, was tested with large samples of patients.

Methods: The Cox proportional hazards regression model was used to compare survival rates among 24,136 non-Hispanic White, and 3,817 Black prostate cancer patients diagnosed between 1986 and 1997, whose cancer had spread beyond the prostate capsule, and who resided in 9 geographic areas covered by the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program of population-based cancer registries. Other analyses involved 5- and 10-year relative survival rates (RSRs) among non-Hispanic White and Black patients diagnosed with distant-stage prostate cancer from 1973 to 1994 (with almost all patients having had a chance to survive for at least 5 years).

Results: The risk of death from prostate cancer was only slightly higher for Blacks than for Whites (adjusted hazard rate ratio = 1.05), when age, extent of disease, tumor grade, marital status, and surgery were included in the Cox proportional hazards regression model. Five- and 10-year RSRs were about 2%-22% higher for Blacks and Whites in strata defined by extent of disease, or among patients with distant stage cancer, but differences were small among married patients.

Conclusions: The findings do not indicate substantial Black-White differences in survival rates of later-stage prostate cancer patients, after adjusting for clinical characteristics and marital status. (Ethn Dis. 2003;13:220–225)

INTRODUCTION

Higher all-cause mortality of statistical significance was reported for 288 African-American (Black) men compared to 975 White men with metastatic prostate cancer, who were all treated with orchietomy in a Southwest Oncology Group (SWOG) randomized clinical trial (comparing orchietomy combined with an anti-androgen to orchietomy and placebo), even after controlling for various prognostic factors in a Cox proportional hazards model (hazard ratio = 1.23). In a subsequent report, after including an indicator of socioeconomic status (SES) at the ZIP code level, the risk ratio for Blacks vs Whites was slightly lower (1.20) and no longer statistically significant (P = .062); however, it was still suggested that “African-American ethnicity may be an independent risk factor for inferior survival in men with metastatic prostate cancer.”

Is this conclusion, drawn from a single clinical trial, supported by data from observational studies? While studies of survival rates using population-based cancer registries cannot provide the same control as clinical trials for co-morbidity and clinical factors, larger samples of late-stage Black prostate cancer patients can be obtained. In a study of 1,032 Black and 1,481 White prostate cancer patients diagnosed between 1977 and 1981 at 11 US comprehensive cancer centers, survival rates differed by race (Black vs White) within stage (local, regional, or distant), but race was not associated to a statistically significant degree with risk of death from all causes in a Cox proportional hazards regression model that included stage and an SES score for the ZIP code of residence.

Brawley and Freeman have emphasized the importance of cause-specific analyses, even in clinical trials, because of residual confounding between race and co-morbidity. Using data from the San Francisco Bay area SEER registry on all prostate cancer patients diagnosed from 1973 to 1993, risk of death from prostate cancer (but not from other causes) was higher, to a statistically significant degree, for 3,338 Blacks compared to 19,996 Whites in a multivariate Cox proportional hazards regression model, after controlling for stage, age, and SES indicators at the census tract level. However, studies are needed from other SEER registries.

Reported SEER-wide data have included another measure of survival, the relative survival rate (RSR), which adjusts for expected mortality in the general population based on age- and sex-specific US death rates for Whites and Blacks (1970, 1980, and 1990). RSRs represent the likelihood that patients will not die from prostate cancer before a specified time (eg, 5 years). SEER reports have indicated small Black-White differences in 5-year RSRs within stage (local-regional, distant, or unknown); however, these data are not stratified by detailed extent-of-disease codes or tumor grade (degree of differentiation).

The present study used large population-based samples from SEER registries to compare survival of Black and non-Hispanic White patients with later-stage prostate cancer. The proportional hazards regression model included variables for extent-of-disease and tumor grade, as well as for the only available socio-demographic variable (ie, marital status), and included separate analyses for deaths from prostate cancer and from all 4 other causes. RSRs for Black and White patients were also calculated for strata defined by extent of disease and marital status.
In a subsequent report . . . it was still suggested that “African-American ethnicity may be an independent risk factor for inferior survival in men with metastatic prostate cancer.”

**Method**

Data from the original 9 SEER registries (Atlanta metropolitan area, Connecticut, Detroit metropolitan area, Hawaii, Iowa, New Mexico, San Francisco-Oakland metropolitan area, Seattle-Puget Sound area, and Utah) established in 1973–1975, were included in the analyses. Excluded were 2 additional registries (both in CA) with data only on cancers diagnosed from 1992–1997. The SEER public-use database includes detailed extent-of-disease codes beginning with cancers diagnosed in 1988. Among all 137,614 Black or non-Hispanic White patients with prostate cancer as their first or only reportable cancer, extent of disease was unknown for only 16,689 (12.1%) patients, with this proportion differing little between Blacks (13.1%) and non-Hispanic Whites (12.0%).

This study focused on later-stage prostate cancer. For those diagnoses made from 1988–1994, extent-of-disease codes 50–85 were selected from clinical and/or operative/pathological assessment (the latter taking precedence) to indicate spread beyond the prostatic capsule. For cancers diagnosed from 1995–1997, 2 fields were available and codes 41–85 for clinical extent (excluding information from prostatectomy) and/or for pathologic extent (information from prostatectomy) were selected to indicate spread beyond the prostate. Using these codes, the sample included 24,136 non-Hispanic White and 3,817 Black patients (total 27,953) diagnosed from 1998–1997 with prostate cancer as their only or first (reportable) cancer, after excluding small numbers of cancers diagnosed solely from death certificates or autopsy reports. Cancers diagnosed in 1998 were excluded due to limited potential follow-up time. Judging from survival rates, patients with unknown stage or extent of disease at diagnosis may have been predominantly late stage; therefore, for some analyses, patients with prostate cancer extending beyond the prostate (N=27,953), and with unknown extent (N=16,689) were combined (total N=44,642).

A Cox proportional hazards regression model was used to analyze risk of death, or hazard ratios (HRs), through the end of 1998, separately for prostate cancer (with deaths from all other causes censored) and for all other causes (with prostate cancer deaths censored). Included in the models was age at diagnosis (<55, 55–64, 65–74, 75–84, and 85+ years). Age <54 was selected because of small samples of younger Black patients (13 Blacks and 70 non-Hispanic Whites were <45 years); models were also run with age in single years or age divided by 5 (results not shown because HRs for race-ethnicity differed little from those tabulated).

The following variables were included in all models. Extent of cancer to viscera, bone, or unspecified metastatic site, was defined by SEER extent-of-disease codes 60–85 for 1988–1994, and 50–85 for 1995–1997. Tumor grade was recoded as 1 or 2 (for low or intermediate grade, or well or moderately differentiated), as 3 or 4 (for high grade, poorly differentiated, undifferentiated, or anaplastic) or as unknown. Tumor grade is a measure of tumor “aggressiveness,” and is an independent indicator of prognosis or survival. Cancer-directed surgery (recoded as prostatectomy vs none, transurethral resection, or unknown) was included as an indicator of accuracy of information on extent of disease. Also, patients selected for surgery and whose cancer was found to be extensive only after surgery (ie, not clinically apparent prior to surgery) would tend to have less extensive cancer and less co-morbidity (or operative risk).

Marital status is coded in SEER as single, married, separated, divorced, widowed, or unknown, and was included in all models. While not intended as a surrogate for SES, marital status does provide some (limited) control for SES, because median income for elderly unmarried men is less than half that for married couples, and rates of poverty or near-poverty are higher for unmarried than for married elderly men. Additional control for SES was not feasible, because only county of residence is included in the SEER public-use database, and an SES variable (poverty rate) by county was not found to be associated with risk of death when added to the regression models, nor did it substantially affect HRs for other variables in the models (data not shown).

Data were also examined for all prostate cancers diagnosed from 1973–1994, with SEER historical stage coded as “distant” (22,868 non-Hispanic Whites and 4,572 Blacks); only diagnoses through 1994 were included, to allow almost all patients an opportunity to survive at least 5 years, for calculation of 5-year RSRs. Distant stage refers to spread beyond regional lymph nodes, and/or to bone or other sites. This sample provides longer potential follow-up, but less-detailed information on staging than is available for the 1988–1997 sample.

Using SPSS, statistical tests for each adjusted death-rate ratio (hazard ratio or HR) involved the calculation of 95% confidence intervals (CIs) that were based on the normal approximation. Analyses of RSRs involved using the same public-use database, and SEERStat 4.0, which produces cumulative RSRs and values for 2 times the standard error (SE) of each RSR. However, with large sample sizes, small dif-
ferences or associations may achieve statistical significance ($P<.05$).

RESULTS

Significant Black-White differences ($P<.001$, chi-square test) were found for distributions of all covariates (data not shown), including age (6.7% Blacks <55 years vs 4.7% non-Hispanic Whites); marital status (55.0% Blacks married vs 76.0% Whites); tumor grade (41.3% Blacks at grade 3 or 4 vs 38.3% Whites); extent of disease, as defined above (68.5% Blacks with spread to viscera or bone, or unspecified metastatic spread vs 50.9% Whites). Mean age was lower to a statistically significant degree ($P<.001$, $t$ test) for Blacks (68.7 yrs, SD=9.52) vs non-Hispanic Whites (70.0 yrs, SD=9.23). With age (<54, 55–64, . . . 85+ years) as the only other covariate in the Cox proportional hazards regression models (not shown), the HRs for Black vs non-Hispanic White race-ethnicity were 1.44 (95% CI=1.36–1.53) for death from prostate cancer, and 1.31 (95% CI=1.22–1.44) for death from all other causes.

When age, extent-of-disease, tumor grade, marital status, and surgery were included in the model (Table 1), the HR for risk of death from prostate cancer (underlying cause) for Black vs non-Hispanic White race-ethnicity was only 1.05 (not statistically significant even for these large samples). HRs were statistically significant for visceral-bone involvement (presence vs absence), tumor grade (high and unknown grade vs low grade), but not for age or marital status.

For causes of death other than prostate cancer, the HR for race-ethnicity for all SEER areas combined was 1.12, slightly higher than the 1.05 figure for death from prostate cancer (Table 1). HRs were statistically significant for age, marital status, and surgery, but not for tumor grade.

The purpose of this study was to examine Black-White differences in survival rates for prostate cancer using a large sample of Blacks, rather than to examine regional variation in the Black-White differences (based on smaller samples). However, the proportion of Black patients differed by SEER area, and overall survival rates for later-stage prostate cancer patients may vary across the SEER areas. When SEER area was added to the models shown in Table 1, with San Francisco-Oakland as the reference category and indicator (categorical) variables for each of the other 8 SEER areas, only one SEER area (New Mexico) had a statistically significant HR (1.13, $P=.045$) for death from prostate cancer, and HRs for Black vs non-Hispanic White race-ethnicity were 1.08 for death from prostate cancer, and 1.08 for death from other causes (data not shown), similar to the corresponding HRs in Table 1.

In separate models (not shown) for each of the 3 SEER areas with $>500$ Black patients, only the San Francisco-Oakland metropolitan area had a statistically significant HR for prostate cancer for Blacks ($N=835$) vs non-Hispanic

### Table 1. Cox proportional hazards regression models for mortality from prostate cancer and other causes among 3,817 Black and 24,136 non-Hispanic White residents of SEER areas diagnosed in 1988–97 with prostate cancer extending beyond the prostatic capsule

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Total Patients</th>
<th>Prostate Cancer (8038 deaths)</th>
<th>Other Causes (5294 deaths)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>No. of deaths</td>
<td>Hazard ratio (CI)</td>
<td>No. of deaths</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
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<tr>
<td>NH White</td>
<td>24,136</td>
<td>6677</td>
<td>1.00 (Referent)</td>
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<tr>
<td>Black</td>
<td>3817</td>
<td>1361</td>
<td>1.05 (0.99–1.12)</td>
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<tr>
<td>Age at diagnosis (yrs)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>1392</td>
<td>271</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>55–64</td>
<td>6320</td>
<td>1370</td>
<td>1.03 (0.90–1.17)</td>
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<td>65–74</td>
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<td>3069</td>
<td>1.00 (0.89–1.14)</td>
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<tr>
<td>75–84</td>
<td>6451</td>
<td>2541</td>
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<tr>
<td>85+</td>
<td>1722</td>
<td>787</td>
<td>1.11 (0.96–1.28)</td>
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<td>Extension to viscera or bone</td>
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<td></td>
</tr>
<tr>
<td>No</td>
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<td>6632</td>
<td>2.93 (2.74–3.12)*</td>
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<td>2409</td>
<td>1.00 (Referent)</td>
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<td>3, 4</td>
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<td>4132</td>
<td>1.66 (1.57–1.74)*</td>
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<td>0.93 (0.95–1.05)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No, unkn.</td>
<td>17,469</td>
<td>7505</td>
<td>4.31 (3.91–4.76)*</td>
</tr>
</tbody>
</table>

* $P<.05$.

CI=confidence interval (95%), rounded to 2 decimals; HR=hazard (death rate) ratio from Cox proportional hazard regression model including all covariates shown; NH=non-Hispanic.

Note: extension to viscera or bone includes SEER extent of disease codes 60–85 for 1988–94 and 50–85 for 1995–97 (see Method section). See Method section for coding of tumor grade.
Whites ($N=3,611$) (HR=1.21, 95% CI=1.06–1.31). For the Detroit area, which had the largest sample of Black patients ($N=1,634$), the HR for prostate cancer death for Blacks vs non-Hispanic Whites was only 0.89 (95% CI=0.80–0.99). For the Atlanta metropolitan area (660 Blacks and 1286 non-Hispanic Whites), the HR was 1.14 (95% CI=0.95–1.38), and not statistically significant.

Other Cox regression models included 16,689 patients with unknown extent of disease (ie, neither clinical nor pathologic), which probably included a disproportionate number of later-stage cancers, for a total of 44,642 patients. HRs (not shown) for Blacks vs non-Hispanic Whites were 1.08 for death from prostate cancer and 1.07, similar to those in Table 1.

The ratio of cumulative RSR up to 5 years after a diagnosis in 1988–1994 for Blacks vs non-Hispanic Whites was 1.03 for extent-of-disease codes 50–56 (extension limited to periprostatic tissue or seminal vesicles), and 1.18 for extent codes 60–85 (extension to adjacent structures, to the pelvic wall or pelvic bone, or to other bones, to soft-tissue or other organs, or unspecified metastasis) (Table 2). For the subgroup of married patients with extensive disease (codes 60–85), the difference between Blacks and non-Hispanic Whites in 5-year RSR was small (ratio=1.14), and the 95% CIs on RSRs overlapped (Table 2).

Other analyses included all patients in the 9 SEER registries diagnosed with distant stage prostate cancer from 1973–1994 (again, because almost all patients had a chance to survive for at least 5 years). Differences between Blacks and non-Hispanic Whites in 5- and 10-year RSRs were small (13%–22%). For 10-year RSRs among married patients, the 95% confidence limits overlapped (Table 2).

All analyses in Table 2 were also performed using all Whites instead of non-Hispanic Whites, with results (not shown) very similar to those shown in Table 2; for example, for 6,249 married Whites diagnosed from 1988–1994 with extent-of-disease codes 60–85, the 5-year RSR was 0.426, identical to that shown in Table 2.

**DISCUSSION**

A potential study limitation of cause-specific analyses of adjusted death-rate ratios (HRs) in Cox proportional hazards regression models is misclassification in assignment of prostate cancer as the underlying cause of death. However, the low HRs for non-prostate-cancer death for both extent of disease and tumor grade variables (Table 1) support the accuracy of cause-of-death coding. In addition, a study of 128 men diagnosed with prostate cancer at ages 58–98 from 1973–1995 who died in 1995 in one of 11 hospitals in King County, Washington, and were included in the Seattle-Puget Sound SEER Registry, reported excellent agreement (97%) between clinician-assigned cause of death (based on review of medical records) and the cause on the death certificate (kappa=0.91).

Another potential study limitation is the use of total US death rates for White, Black, and other groups to obtain expected mortality in calculating RSRs by SEER computer programs for comparisons of Blacks and non-Hispanic Whites, because expected mortality rates in the general population by Hispanic ethnicity are not included. However, analyses using all Whites instead of non-Hispanic Whites produced results similar to those shown in Tables 1 and 2.

Another potential limitations is that better diagnostic work-ups in Black compared to non-Hispanic White patients could lead to less complete and less accurate staging in. However, analyses with patients having both extensive disease and unknown extent of disease at diagnosis produced results similar to those shown in Table 1. In addition, less accurate staging in Blacks should have resulted in lower RSRs for Black compared to non-Hispanic White patients with limited extension (ie, only to periprostatic tissues or seminal vesicles), if
this group actually included a pool of Black patients with more-extensive, yet undetected, cancers; however, this was not supported by the small differences in RSRs between Blacks and non-Hispanic Whites (Table 2).

Within these limitations, using large samples from population-based US cancer registries, this study found only small differences in risk of death (in the Cox proportional hazards regression model with a number of covariates, Table 1) from prostate cancer between Black and non-Hispanic White patients whose prostate cancer was diagnosed at later stage. The strong associations between risk of death from prostate cancer and both extent of disease and tumor grade are not unexpected. The association between the absence of a prostatectomy and higher risk of death from causes other than prostate cancer (Table 1) suggests that this variable provides some control for co-morbidity (which affects selection for surgery, independent of age). The HR for prostate cancer was only slightly lower for married vs single patients (Table 1); slightly larger associations have been reported in some studies,11 but this study included a number of covariates in the model (Table 1). The lower HR for causes other than prostate cancer for married vs single patients is consistent with the literature.11

The finding of an elevated HR from prostate cancer for later-stage Black vs non-Hispanic White patients in the San Francisco-Oakland metropolitan area in this study is noteworthy in view of a report from the San Francisco Bay area registry demonstrating that mortality from prostate cancer (and not other causes) was higher for Blacks than Whites (all stages combined), when age, stage, and SES indicators at the census tract level were included in the models.5 This finding was not true for 2 other SEER areas (Detroit and Atlanta metropolitan areas) with large numbers of Black patients, which could be due to chance, regional differences in the assignment of underlying cause of death, or other factors affecting Black-White differences in survival.

The slightly elevated HRs for prostate cancer in the regression model (Table 1), and higher RSRs (Table 2) for Blacks vs non-Hispanic Whites, could be due to chance or residual confounding effects of SES. Additional analyses from observational studies would help determine this. The Prostate Cancer Outcomes Study, initiated in 1994, has reported Black-White differences in stage at diagnosis,12 and future analyses should include stage-specific survival comparisons, controlling for SES indicators at the individual (patient) level; however, the sample size for Blacks is limited (ie, 539, all clinical stages combined).

The approximately 20% Black-White difference in survival of metastatic prostate cancer found by a single clinical trial12 could be due to chance, residual confounding by SES, and/or co-morbidity,12-14 or could represent a finding restricted to patients with orchiectomy. Orchiectomy and hormone therapy are not included on the SEER public-use file.7 Generally, Black patients are less likely than Whites to receive extensive, and/or expensive, cancer treatments for prostate and other cancers, although findings are not consistent across studies.15 If such treatments improved survival for late-stage prostate cancers, which is uncertain,15 then including treatment-related variables in the Cox proportional hazards regression model could reduce even further the small Black-White differences in risk of death found in this study.

Additional Black-White comparisons are needed from clinical trials on treatments for prostate cancer that extends beyond the prostatic capsule. Such studies should consider the confounding effects of SES, preferably using patient-specific data on SES. A report from a clinical trial of patients with another type of cancer, advanced non-small cell lung carcinoma, indicated that adjustment for marital status, income, and other socio-demographic indicators, along with clinical-prognostic features at diagnosis, removed the Black-White survival difference; however, complete information was available for only 30 of 46 Black patients.16 The Clinical Trial Consensus Panel of the National Medical Association has recommended more extensive studies of certain cancers (including prostate) among minority groups, to address racial-ethnic differences in susceptibility, diagnostic factors, and treatment17; survival and other outcomes also should be assessed.

Suggestions of biological explanations for small apparent racial-ethnic differences in stage-specific survival or treatment efficacy12 should be interpreted with caution, due to the possible residual confounding effects of SES and co-morbidity. With regard to genetic explanations, the limited genetic variation between US Blacks and Whites is of uncertain significance in explaining differences in disease risk, prognosis, and responses to treatments.18 The African-American Hereditary Prostate Cancer Study, involving the collaboration of Howard University and a predominantly African-American group of urolo-
gists,\textsuperscript{18} may provide resources for investigating genetic factors in disease risk, along with cohorts for studies of outcomes, including survival.

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REFERENCES


AUTHOR CONTRIBUTIONS
Design and concept of study: Polednak
Acquisition of data: Polednak
Data analysis and interpretation: Polednak
Manuscript draft: Polednak
Statistical expertise: Polednak